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# Novel Sythesis Method for 2-Methylpyrazine-5-Carboxylic acid Using Acetone Aldoxime

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***Abstract:*** **- The title commercially important molecules are obtained utilizing smart synthetic methodologies. Herein, novel syntheses are reported in environmental friendly syntheses than reported earlier Organic reaction methodologies with better yield and purity.**

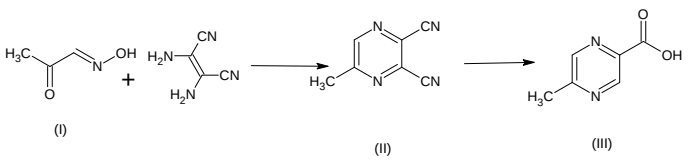
**Keywords: 2-Methylpyrazine-5-Carboxylic acid, Acetone Aldoxime**

## INTRODUCTION

-Methylpyrazine-5 -Carboxylic acid is an important key intermediate for Glipizide drug. N - Oxide derivative of 2-Methyl Pyrazine 5 - Carboxylic acid is Acipimox, a valuable compound used as Antilipemic and Hypolipidemic agents**1,2,3** . 2-Methyl pyrazine-5-carboxylic acid has been prepared by several known methods mentioned in literature. One such known method is described by Zhang, Ruikuan**4** wherein, o – Phenylenediamine is condensed with pyruvic aldehyde in presence of Sodium Hydrogensulfite, oxidized by KMnO4 / K2Cr2O7 and decarboxylated with H2SO4 to give 2-Methylpyrazine- 5 - carboxylic acid. Foa Marco (IT)**5** in 1992 disclosed electrochemical oxidation of 2 – methyl 5 - oxomethylpyrazine using NiO(OH) with 74 – 93 % yield of 2-Methyl Pyrazine 5 - Carboxylic acid with limited commercial success. Another method described by G.B.Barlin**6** wherein, 2 - Methyl Pyrazine 5 - Carboxylic acid is prepared by direct oxidation of 2, 5 - dimethyl pyrazine with limited success. In this reaction pyrazine 2, 5 - dicarboxylic acid is also getting formed as one of the by products. E. Felder**7** disclosed method which gives mixture of 2 – methyl pyrazine 5 - carboxylic acid and 2 - methyl pyrazine 6 - carboxylic acid when 2, 3 - diamino propionic acid is reacted with methyl glyoxal. Again, it is not commercially useful method.

Another process for preparation of 2-Methyl Pyrazine 5 - Carboxylic acid is disclosed by Pietro Giardino**8** which involves condensation of diamino malenonitril with Pyruvic aldehyde in aqueous ethyl alcohol and acetic acid to give 2,3-dicyano 5 –Methylpyrazine which is hydrolized in dilute suphuric acid and the resultant product decarboxylated insitu , to obtain desired product with 40 -45 % yield. In this process pyruvic aldehyde used as starting material is not easily accessible and available relatively at high price. Thus, there is need to improve the process by using low cost and easily accessible material acetone aldoxime in place of pyruvic aldehyde.

. 2-Methylpyrazine-5-Carboxylicacid is prepared by condensing diaminomaleonitrile with acetone aldoxime in presence of dilute inorganic acid and resultant product thus obtained, is hydrolysed followed by selective insitu decarboxylation of 2, 3 - dicyano 5 - methylpyrazine in aqueous acid. Process for the preparation of 2-Methyl Pyrazine 5 - Carboxylic acid involves three steps process: (i) Reaction of isopropyl nitrite with acetone in presence of concentrated acid. (ii) Reaction of diaminomaleonitrile with acetone aldoxime in presence of dilute acid and (iii) Hydrolysis followed by selective insitu decarboxylation of 2, 3 - dicyano 5 - methyl pyrazine in aqueous acid. Herein, we describe innovative process for preparation of pure 2-Methyl pyrazine 5 - Carboxylic acid of formula (I) in good purity and yield from starting material i.e. acetone aldoxime(III), which is prepared in good yield by reaction of isopropyl nitrite with acetone in presence of concentrated acid. Thus, acetone aldoxime is condensed with diaminomaleonitril in presence of dil. acid to give 2, 3 - dicyano 5 - methyl pyrazine of formula (II). It is further hydrolyzed in aqueous acid and decarboxylated insitu to obtain 2 - methylpyrazine 5 - Carboxylic acid of formula (I) as shown in scheme 1.




**Reaction Scheme - 1**

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## EXPERIMENTAL

**General Remark:** All chemicals were purchased from Merk and Fluka, Solvent used as received of commercial grade. Equipments like overhead stirrer, four necks round bottomed flask with thermo well, condenser and heating bath was used to carry reaction. Progress of reaction was monitored with TLC SILG/UV 254 plate. Product was characterized by comparison of their IR, 1HNMR, Mass spectra reported in literature.

Example:

**1. Preparation of Acetone aldoxime (I)**

In a 4 necked round bottom flask equipped with dropping funnel and over head stirrer were placed 232.32 gm, (4.0 moles) of acetone and chilled it to + 5 °C. 3 gm of cone, hydrochloric acid was added at 0 °C to 10 °C into reaction mass, 89.1 gm (1 mole) of isopropyl nitrite solution was added drop wise through dropping funnel at 10 to 15 °C. The reaction mass was stirred further at 10 - 30 °C for 1-2 hour. The excess acetone and isopropyl alcohol formed were distilled out under vacuum 30- 60 °C to get crystalline mass 76.77 gm of Acetone aldoxime (III) with 83 - 88 % yield and 98% purity by GLC.

**2. Preparation of 2,3- dicyano 5 - methyl pyrazine (II)**

In a 4 necked round bottom flask equipped with dropping funnel and over head stirrer reflux condenser and thermowell were placed 500 ml of water to it add 100 gms (0.926 moles) of diaminomalenonitrile (DAMN) with stirring at 30 °C. In to mixture, 92 ml 50 % sulphuric acid (v/v) was added drop wise through dropping funnel at 30 °C. The reaction mass was heated at 50 - 80 °C. Then 105 gm (1.1-1.2 moles) of acetone aldoxime preheated for 30 min in 500 ml water and 84 gms sulphuric acid at 50-70 °C was added drop wise during 0.5-1 hour maintaining reaction temperature 80 °C. The reaction mass was maintained at same temperature for 1 -2 hours. The progress of the reaction was monitored by thin layer chromatography (TLC). Reaction mass was cooled to 25 °C and extracted with toluene. The combined extracts were washed with water and distilled off toluene under reduced pressure to give solid 100 gm of **2,3- dicyano 5 - methyl pyrazine (II)** in 75 % yield with 98 % purity. (M.P = 98-100 °C.)

**3. Preparation of 2 - Methyl Pyrazine 5 - carboxylic acid (III)**

In a 4 necked round bottom flask equipped with dropping funnel and over head stirrer were placed 900 ml of 50 % v/v sulphuric acid to it added 100 gms (0.694 moles) 2, 3 - dicyano 5 - methyl pyrazine at 30 °C. The reaction mass was heated to 70-100 °C and maintained for 3-5 hours. The progress of the reaction was monitored by HPLC/TLC. After completion of reaction, reaction mass was cooled to 5 to 10 °C and 40 % caustic lye solution was added to adjust pH 2 - 3 and extracted with methyl ethyl ketone. The combined extracts were washed with saturated sodium chloride solution and distilled off methyl ethyl ketone under reduced pressure to give crude solid product weighed 55-60 gm which was crystallized by water to obtain 45-50 gm (46 - 52% yield) pure 2 - methylpyrazine 5 - Carboxylic acid(III). It was analyzed by High Performance Liquid Chromatography (HPLC) for its purity (melting point = 163 -165 °C.) The product obtained was characterized by elementary analysis, IR and NMR

## RESULTS

1) Acetone aldoxime (I) = Yield 76.77 gm (83 - 88 %), Purity- 98% (GC)

2) 2,3- dicyano 5 - methyl pyrazine (II) = Yield 100 gm ( 75 %) Purity- 98%

3) 2 - methylpyrazine 5 - Carboxylic acid(III) = Yield 50 gm ( 52 %) Purity- 98% (HPLC)

## CONCLUSION

A novel method of synthesis with better yield and high purity commercially important molecule is obtained by utilizing simple synthetic methodologies. Generally reported processes involved with low yield and less selectivity in presence of costly metal catalyst. The process can be used in large scale chemical manufacturing industries. The developed process for 2 - methylpyrazine 5 - Carboxylic acid as an important drug intermediate for Glipizide/ Acipimox at normal and mild reaction conditions through acetonealdoxime and readily available diamino maleonitrile as raw material

## REFERENCES

1. Dahlstrom Mikael, patent – EP 0149592, 1985.
2. Cooney Mark (US); patent - US2005261312, 2005.
3. Caudill Jonathan (US); patent - US2005239803, 2005.
4. Zhang, Ruikuan. Faming Zhuanli Shenqing Gongkai, Shuomingshu CN, 2003,
5. 1392143, 7 pp,
6. Foa Marco et al, (IT) ; US patent, 5091066, 1992.
7. G.B.Barlin “The Pyrazines” John Wiley Ed. Page, 1982, 79.
8. E.Felder et al, in Chem Ber, 1967, 100, 555-559 .
9. Pietro Giardino et al, GB2099820 A, 1982.