Preparation of Highly Pure N, N'-Bis-(2-aminoethyl)-1, 2-ethanediamine

G. Panchapakesan, R. Venkatragavan, P. Venkataramana Reddy,
T. Lakshminarayana, E. Balaiah, G. Jayaprasad,
*G. Navaneethakrishnan and P. Muthukrishnan**
Nuray Chemicals Private Limited, Plot no, 111, SIDCO Industrial Estate,
Kakkalur, Tiruvallur, Tamilnadu-602003, India.
Email: muthukrishnan.p@nuraychemicals.com

Abstract: N, N'-Bis (2-aminoethyl)-1, 2-ethanediamine hydrochloride salt is a chelating compound which is used for removal of excess of copper from the body. This compound prepared by previous methods having low purity. The present study provided the preparation of highly pure Polyamine hydrochloride by production of Schiff base (Polyamine adduct) by treating Boc-protected polyamine with aldehyde followed by deprotection and salt formation. The compound prepared by the present study having higher level of purity and it is suitable for pharmaceutical substance.

Keywords: Polyamine, Ethanediamine, Chelating Agents, Excess copper

I. INTRODUCTION

The compound N, N'-bis (2-aminoethyl)-1, 2-ethanediamine (polyamine) and its analogues are copper antagonists. The polyamine is copper chelating agents and it is used sometime as an epoxy curing agents [1]. It is also used as lubricating oil additives, analytical agents to identify copper and nickel and used as a thermosetting resin. There are wide ranges of synthesis methods available for the preparation of polyamine [2]. Since it is straight chain alkylamine, other straight and branched amines and cyclic amines which otherwise called as impurities formed very easily during the preparation of this compound. The formation of unwanted impurities to be controlled or suitable purification methods should be adopted for the preparation of pharmaceutical grade product. For a pharmaceutical chemist, it is exciting task for isolating pharmaceutical grade polyamine which having acceptable level of impurities. The present study preparing the highly pure pharmaceutical grade polyamine compounds which having very less amount or even no detectable amount of impurities. The present study provides preparation of highly pure polyamines by preparing Polyamine adduct, removing the unwanted impurities and deprotecting the protected amines to obtain highly pure pharmaceutical grade polyamine.

II. MATERIALS AND METHODS

The starting materials such as Boc-protected polyamine used for the preparation of polyamine compounds of the present study can be prepared by method as known in the literature [3, 4] by the reacting ethylenediamine (purchased from Diamines and Chemicals Limited, Vadodara-391346 India) with chloroacetonitrile (purchased from AMI Organics Pvt. Ltd, Surat-394230, India) to obtain dinitrile compound which is than treated with DiBoc to obtain Boc-protected dinitrile. Ravikumar *et al* [5] disclosed a process of protecting amine with Boc group in the 2-aminoacetonitrile followed by reduction of nitrile group to obtain Boc-protected amine. Burkhard Klenke and co-workers are established the reduction of nitrile groups in the presence of Boc-Protected amino groups by catalytic hydrogenation by Raney-nickel catalyst [6]. The polyamine prepared by the above known methods having impurities such as straight chain and cyclized amine impurities. In the present study the Boc-protected polyamine converted in to Polyamine adduct by reaction with aldehyde which is than deprotected by using acid to get the pure polyamine acid salt which having pharmaceutical grade purity and having low level of impurities. The synthetic scheme of the above reaction is as given below.

The identification and purity of the products was checked by using High Performance Liquid Chromatography (HPLC) with suitable mobile phase. The ^{1}H NMR spectra were recorded on a Bruker Avance II 400 NMR spectrometer with DMSO and $CDCl_3$ as solvents and TMS as an internal standard. The chemical shifts were expressed in δ (ppm) values.

III. RESULTS AND DISCUSSION

The present study provides the preparation of highly pure Polyamine hydrochloride by production of Polyamine adduct by treating Boc-protected polyamine with aldehyde followed by deprotection and salt formation. The compound prepared by the present study having higher level of purity and it is suitable for pharmaceutical substance. In the present study the new purification method was adopted to enhance the purity of polyamine compounds which is also suitable for the purification of other straight chain polyamine compounds like ethylenediamine, diethylenetriamine, tetraethylenepentamine. The present study provides preparation of highly pure polyamines by preparing Polyamine adduct, removing the unwanted impurities by extraction and crystallization than deprotecting protected amines to obtain highly pure pharmaceutical grade polyamine.

The polyamine compound of formula 1 of present study can be prepared by following the reaction sequences.

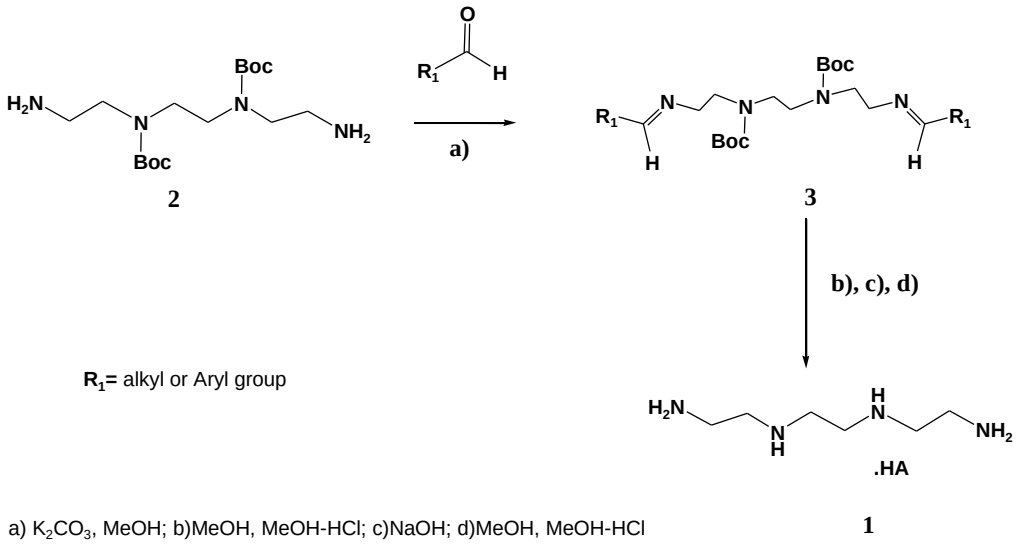

Fig-I: Synthetic pathway for the preparation of polyamine compound of (1)

Reagents: a) K_2CO_3, MeOH; b)MeOH, MeOH-HCl; c)NaOH; d)MeOH, MeOH-HCl

Synthesis of [2-(benzylidene-amino)-ethyl]-(2-{[2-(benzylidene-amino)-ethyl]-tert-butoxy carbonyl-amino}-ethyl)-carbamicacid tert-butyl ester (3):

To a compound **2**, 500 mL of methanol, 163 g of potassium carbonate were added and cooled to 0-10 °C. To the reaction mass 125 g of phenylmethanal was added and stirred at room temperature. After completion of the reaction the reaction mass was cooled to 10 °C and the obtained solid was filtered, washed with water and suck dried to obtain 264 g of [2-(benzylidene-amino)-ethyl]-(2-{[2-(benzylidene-amino)-ethyl]-tert-butoxycarbonyl-amino}-ethyl)-carbamic acid tert-butyl ester (**3**).

Synthesis of N^1-[2-(2-amino-ethylamino)-ethyl]-ethane-1, 2-diamine tetrahydrochloride:

A compound (**3**) and 1000 mL of methanol were stirred, methanolic hydrochloride was added and the reaction mass was heated to 65 °C for 4 hours. After completion of the reaction, the reaction mass was cooled to 0 °C and the obtained solid was filtered. The obtained solid was washed with methanol and dried under vacuum at room temperature for 12 hours to obtain 99 g of N^1-[2-(2-amino-ethylamino)-ethyl]-ethane-1, 2-diamine tetrahydrochloride.

Synthesis of N^1-[2-(2-amino-ethylamino)-ethyl]-ethane-1, 2-diamine dihydrochloride (1):

To a 400 mL of 35% sodium hydroxide solution, 450 mL of n-butanol was added, 40 g of N^1-[2-(2-amino-ethylamino)-ethyl]-ethane-1, 2-diamine tetrahydrochloride was added at room

temperature and stirred for 1 hour. To the reaction mass aqueous methanol was added and pH was adjusted to neutral by using methanolic hydrochloride solution. To the clear solution, 200 mL of acetonitrile was added, stirred for 2-5 hours at 5 ºC. The obtained solid was filtered, washed with acetonitrile and dried to obtain 21 g of N^1-[2-(2-amino-ethylamino)-ethyl]-ethane-1, 2-diamine dihydrochloride. The obtained compound was slurried with mixture of isopropanol and methanol to get the pure title compound (**1**). Purity 99.98 % by HPLC.

IV. CONCLUSION

The compound polyamine dihydrochloride prepared by methods as described in this paper having higher level of purity and having individual impurity not more than 0.02% by HPLC analysis which is not attained by any other known methods. This compound used as a pharmaceutical product which meets the regulatory submissions and provides better bioavailability since it is highly pure. The present purification method is cost effective, suitable for large scale preparation and economically viable. This study provides researchers to evaluate the better purification methods for a compound like a present study and other complexed compounds.

V. ACKNOWLEDGMENT

The authors are thankful to management, analytical department and other departments of Nuray Chemical Private Limited for providing support and data.

REFERENCES

[1] “Merck Index,” p. 9478 (10th Edition, 1983).

[2] Giffin D. Jones, Arne Langsjoen, Sisterm Ary Marguerite Christine Neumann, and Jack Zomlefer, “The polymerization of ethylenimine,” J. Org. Chem. 1944, 9(2), 125-147.

[3] Julie A. Spicer, Swarna A. Gamage, Graeme J. Finlay and William A. Denny, “Synthesis and Evaluation of Unsymmetrical Bis(arylcarboxamides) Designed as Topoisomerase-Targeted Anticancer Drugs,” Bioorg Med Chem, 2002, 10; 19–29.

[4] Jerald S. Bradsha &, Krzysztof E. Krakowisk and Reed H. Izatt, “Preparation of diamino ethers and polyamines,” Tetrahedron 1992, 48, 4475-4515.

[5] Vasulinga T. Ravikumar, "A convenient large scale synthesis of N-Boc ethylenediamine," Synthetic Communications 1994, 24(12), 1767- 1772.

[6] Burkhard Klenke and Ian H. Gilbert, "Nitrile Reduction in the Presence of Boc-Protected Amino Groups by Catalytic hydrogenation over Palladium-Activated Raney-Nickel," J. Org. Chem. 2001, 66, 2480-2483.