(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 March 2017 (23.03.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/046695 A1

(51) International Patent Classification:
C07C 209/44 (2006.01) *C07C 209/00* (2006.01)
C07C 211/14 (2006.01)

(21) International Application Number:
PCT/IB2016/055439

(22) International Filing Date:
13 September 2016 (13.09.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
3560/MUM/2015 18 September 2015 (18.09.2015) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2017/046695 A1

(54) Title: AN IMPROVED PROCESS FOR PREPARATION OF TRIENTINE DIHYDROCHLORIDE

(57) Abstract: The present invention provides a process for preparation of trientine dihydrochloride (1) comprising reaction of protected triethylene tetramine with hydrochloric acid in an aqueous system to yield the dihydrochloride salt wherein the formation of inorganic impurities and undesired salts is controlled significantly.

AN IMPROVED PROCESS FOR PREPARATION OF TRIENTINE DIHYDROCHLORIDE

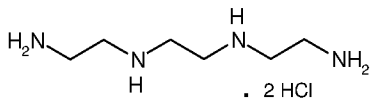
This application claims the benefit of Indian Provisional Application No.3560/MUM/2015, filed on 18th September 2015, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to a process for the preparation of trientine hydrochloride having desired purity. Specifically, the invention relates to a process for preparation of trientine dihydrochloride (1) comprising the reaction of protected triethylenetetramine with hydrochloric acid in an aqueous medium to directly yield the corresponding dihydrochloride salt having desired purity.

BACKGROUND OF THE INVENTION

Trientine, chemically known as triethylenetetramine or N,N'-bis(2-aminoethyl)-1,2-ethanediamine belongs to the class of polyethylene polyamines. Trientine dihydrochloride is a chelating agent which is used to bind and remove copper in the body in the treatment of Wilson's disease.



Trientine dihydrochloride (1)

Trientine dihydrochloride formulation, developed by Aton with the proprietary name SYPRINE, was approved by USFDA on November 8, 1985 for the treatment of patients with Wilson's disease, who are intolerant to penicillamine. Trientine dihydrochloride, due to its activity on copper homeostasis, is being studied for various potential applications in the treatment of internal organs damage in diabetics, Alzheimer's disease and cancer.

Various synthetic methods for preparation of triethylenetetramine (TETA) and the corresponding dihydrochloride salt have been disclosed in the prior art.

U.S. 4,806,517 discloses the synthesis of triethylenetetramine from ethylenediamine and monoethanolamine using Titania supported phosphorous catalyst while U.S. 4,550,209 and U.S. 5,225,599 disclose catalytic condensation of ethylenediamine and ethylene glycol for the synthesis of linear triethylenetetramine using catalysts like zirconium trimethylene diphosphonate, or metatungstate composites of titanium dioxide and zirconium dioxide.

U.S. 4,503,253 discloses the preparation of triethylenetetramine by reaction of an alkanolamine compound with ammonia and an alkyleneamine having two primary amino groups in the presence of a catalyst, such as supported phosphoric acid wherein the support is comprised of silica, alumina or carbon.

The methods described above for preparation of triethylenetetramine require high temperatures and pressure. Further, due to the various possible side reactions and consequent associated impurities, it is difficult to control the purity of the desired amine.

CN 102924289 discloses a process for trientine dihydrochloride comprising reduction of N,N'-dibenzyl-,N,N'-bis[2-(1,3-dioxo-2H-isoindolyl)ethyl]ethanediamine using hydrazine hydrate to give N,N'-dibenzyl-,N,N'-bis(2-aminoethyl)ethanediamine, which, upon condensation with benzyl chloroformate gave N,N'-dibenzyl-,N,N'-bis[2-(Cbz-amino)ethyl]ethanediamine, and further reductive deprotection to give the desired compound.

CS 197,093 discloses a process comprising reaction of triethylenetetramine with concentrated hydrochloric acid to obtain the crystalline tetrahydrochloride salt. Further reaction of the salt with sodium ethoxide in solvent ethanol, filtration of the solid sodium chloride which is generated in the process, followed by slow cooling and crystallization of the filtrate provided the dihydrochloride salt. Optionally, aqueous solution of the tetrahydrochloride salt was passed through a column of an anion exchanger and the eluate containing free base was treated with a calculated amount of the tetrahydrochloride, evaporated, and the residue was crystallized from aqueous ethanol to yield the dihydrochloride salt.

The process is quite circuitous and cumbersome, requiring use of strong bases, filtration of sodium chloride and results in yields as low as 60%.

US 8,394,992 discloses a method for preparation of triethylenetetramine dihydrochloride wherein tertiary butoxycarbonyl (boc) protected triethylenetetramine is first converted to its tetrahydrochloride salt using large excess of hydrochloric acid in solvent isopropanol, followed by treatment of the resulting tetrahydrochloride salt with a strong base like sodium alkoxide to produce the amine free base (TETA) and sodium chloride salt in anhydrous conditions. The free amine is extracted with tertiary butyl methyl ether (TBME), followed by removal of sodium chloride salt and finally the amine free base TETA is treated with hydrochloric acid in solvent ethanol to give trientine hydrochloride salt.

The method suffers from the following drawbacks.

a) Lengthy process comprising treatment of tetrahydrochloride salt with a base in anhydrous conditions to obtain the amine and its further conversion to TETA dihydrochloride, which includes a number of unit operations such as solvent extraction, washing of filtered solid, solvent concentration, crystallization at various stages of synthesis etc.

b) Use of excessive amounts of hydrochloric acid as well as anhydrous alcoholic and ether solvents.

c) Stringent requirement of complete removal of sodium chloride formed during the process. If the salt is not scrupulously removed, the final product, trientine hydrochloride salt is unlikely to pass the sulphated ash test, which is indicative of complete removal of inorganic impurities from the drug product.

Thus it would be evident that there still exists a need for a convenient, cost effective, and industrially viable process for synthesis of triethylenetetramine dihydrochloride (1) which avoids the following.

a) lengthy synthetic routes for protection and deprotection of the reactant amines and intermediates,

b) excessive use of organic solvents,

c) use of mineral acids in multiple steps

The process further eliminates use of strong bases, as well as controls the number of unit operations, and yet provides the desired dihydrochloride in substantially pure form in good yield.

The present inventors have developed a novel process for synthesis of triethylenetetramine dihydrochloride (1) comprising a single step of treating Boc-protected amine (6) with hydrochloric acid to give the desired dihydrochloride salt (1) in substantially pure form and in good yield.

In this way, the present inventors have developed a convenient and cost-effective process by skillfully manipulating the deprotection, salt formation and isolation steps in the synthesis of desired dihydrochloride (1). The method avoids lengthy synthetic steps, strong bases, excessive use of organic solvents, use of multi-molar equivalents of mineral acid and most significantly eliminates the possibility of traces of inorganic salts in the final product. The use of hydrochloric acid in sub-equimolar quantities for simultaneous deprotection and salt preparation reaction results in selective formation of the dihydrochloride salt.

OBJECT OF THE INVENTION

An objective of the present invention is to provide triethylenetetramine dihydrochloride of formula (1) having desired purity by a convenient and economical process which does not involve excessive quantities of organic solvents and hydrochloric acid.

Another object of the present invention is to provide an efficient process for preparation of triethylenetetramine dihydrochloride (1), wherein Boc-protected triethylenetetramine (6) is treated with sub-equimolar quantities of hydrochloric acid in aqueous system to provide the dihydrochloride salt directly in a single step.

SUMMARY OF THE INVENTION

The present invention relates to a method for synthesis of triethylenetetramine dihydrochloride of formula (1) in substantially pure form.

An aspect of the invention relates to the reaction of tert-butyl N-(2-aminoethyl)-N-2-[(2-aminoethyl)(tert-butoxy)carbonyl]amino]ethyl}carbamate of formula (6) with hydrochloric acid in aqueous system in the temperature range of 80-110^{0}C to give triethylenetetramine dihydrochloride (1).

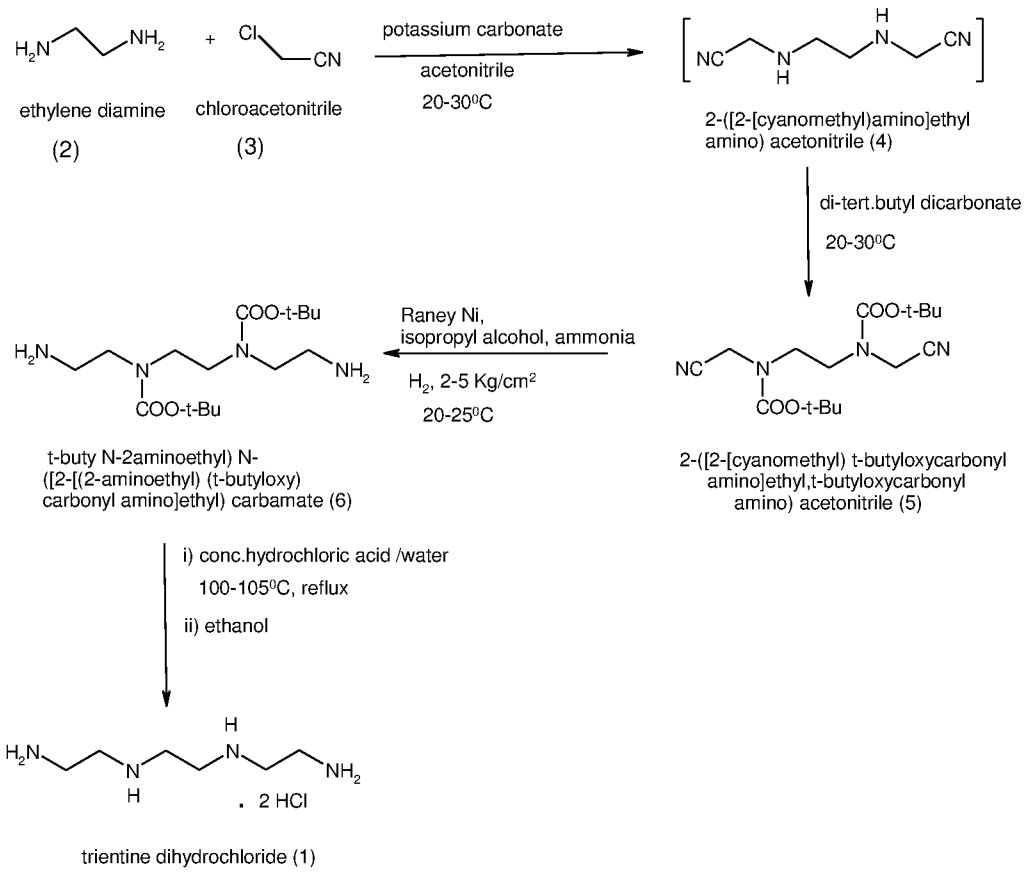
The objectives of the present invention will become more apparent from the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

The present inventors, in their pursuit for developing a convenient, commercially viable and economical process for obtaining trientine dihydrochloride conforming to regulatory specifications, carried out extensive experimentation aimed at minimizing the synthetic steps as against the circuitous routes disclosed in prior art. Surprisingly, it was observed that a direct, single-step process for preparation of the dihydrochloride salt was possible when the reaction of tertiary butoxycarbonyl protected amine (6) with hydrochloric acid was carried out in an aqueous system at 80 to 110^0C in the pH range of 7-8. In this reaction, hydrochloric acid which was used in less than molar equivalent quantities with respect to the protected amine reactant, served the dual purpose of deprotection of the protecting group and formation of the salt, providing the selective dihydrochloride formation. It was also observed that the reaction could be carried out either at mild pressure in an autoclave or at atmospheric pressure.

This novel strategy thus avoids lengthy, time consuming reaction sequence of preparing tetrahydrochloride salt from the protected diamine, its conversion to trientine free base, followed by re-conversion to the dihydrochloride salt by reaction with hydrochloric acid. Consequently, use of multi-molar equivalents of hydrochloric acid, excessive organic solvents and the multiple unit operations at intermediate stages are avoided to give a convenient and robust process for the dihydrochloride salt (1) which conforms to regulatory requirements.

A noteworthy part of the embodied method was that there was no formation of sodium chloride during the process, due to which the unit operations for separation and filtration of the salt were eliminated and more importantly, problems associated with sulphated ash content, which hampered the purity of the final product; dihydrochloride salt were avoided.



Scheme 1: Method embodied in the present invention for the preparation of triethylenetetramine dihydrochloride (1)

In an embodiment, tert-butyl-N-(2-aminoethyl)-N-2-[(2-aminoethyl)-(tert-butoxy)carbonyl] amino]ethyl} carbamate of formula (6) was treated with concentrated hydrochloric acid.

The amount of hydrochloric acid employed for deprotection of the amine group and subsequent dihydrochloride formation was in the range of 1.6 to 2.1 equivalents with respect to the tertiary butoxycarbonyl-protected diamine (6).

It was noted that if, during the reaction eventually the pH was excessively higher or lower than the range of 7 to 8, there were problems in isolating the desired dihydrochloride salt resulting in substantial yield loss.

The reaction mixture was heated in the temperature range of 80-110°C.

The reaction was carried out at atmospheric pressure or in a pressure vessel (autoclave) wherein the pressure was maintained in the range of 2-10 Kg/cm^2.

After completion of the reaction as monitored by TLC, the aqueous reaction mixture was concentrated and ethanol was added to the residue. The resultant mixture was heated till a clear solution was obtained. Further cooling of the reaction mixture, filtration and drying yielded the desired compound, triethylenetetramine dihydrochloride (1) with yield around 80% and purity ≥98% (purity within USP limits).

Compound (6) was prepared following known methods by reaction of ethylene diamine (2) with chloroacetonitrile (3) using potassium carbonate as base and solvent acetonitrile to give 2-({2-[(cyanomethyl)amino]ethyl}amino) acetonitrile (4). Compound (4) was further treated with di-tertiarybutyl dicarbonate and the resulting boc-protected dinitrile (5) was hydrogenated using Raney nickel, ammonia and isopropyl alcohol to yield compound (6).
Alternatively, the preparation of compound (4) and its further reaction with ditertiarybutyl dicarbonate was carried out in-situ.

The following examples are meant to be illustrative of the present invention. These examples exemplify the invention and are not to be construed as limiting the scope of the invention.

EXAMPLES

Example 1: Preparation of 2-([2-[cyanomethyl]-t-butyloxycarbonylamino]ethyl- t-butyloxy carbonylamino)acetonitrile (5)

Potassium carbonate (481.9 g) was added to a stirred mixture of ethylenediamine (100.0 g) in acetonitrile (800 ml) and cooled to around 10^0C. Chloroacetonitrile (263.8 g) was gradually added at same temperature and stirred at 25-30^0C, till completion of the reaction, as monitored by HPLC. The mixture was cooled to 5-15^0C and Boc-anhydride (762.1g) was added to it, followed by stirring at the same temperature. The temperature was raised to 25-30^0C and the mass was stirred till completion of the reaction, as monitored by HPLC.

The reaction mass was filtered and the filtrate was concentrated. Toluene was added to the residue, and the mixture was heated to around 70^0C followed by cooling and filtration to give 2-([2-[cyanomethyl)-t-butyloxycarbonylamino]ethyl-t-butyloxycarbonylamino) acetonitrile (5).

Yield: 506.8 g

% Yield: 89.9 %

Example 2: Preparation of t-butyl(N-2-aminoethyl)N-([2-[(2-aminoethyl)t-butyloxy)carbonylamino] ethyl) carbamate (6)

Raney nickel (120.0 g) in isopropanol (100 ml) was charged into an autoclave, followed by a mixture of Compound 5 (200 g) in isopropanol (400 ml). Cooled ammonia solution prepared by purging ammonia gas in 1400 ml isopropanol, equivalent to 125 g ammonia was gradually charged to the autoclave and the reaction was carried out around 15-25^0C under hydrogen pressure of 2-5 Kg/cm^2.

After completion of the reaction, as monitored by HPLC, the mass was filtered, concentrated, and methyl tertiary butyl ether was added to the residue. The mixture was heated to around 50^0C, followed by cooling of the mass, stirring, optional seeding with compound 6 and filtration to give tertiary butyl-(N-2-aminoethyl)N-([2-[(2-aminoethyl)-(tert-butyloxy) carbonylamino] ethyl) carbamate.

Yield: 174 g

%Yield: 85 %

Example 3: Preparation of triethylenetetramine dihydrochloride (1)

Concentrated hydrochloric acid (121.5 g) was gradually added to a stirred mixture of tertiary-butyl-N-(2-aminoethyl)-N-2-[(2-aminoethyl)-(tert-butoxy) carbonyl] amino] ethyl} carbamate (Compound 6, 200.0 g) and water (1400 ml) at 20-30^0C. The reaction mixture was heated in the temperature range of 100-105^0C till completion of the reaction, as monitored by HPLC, with optionally distilling out water, if so required.

The reaction mass was concentrated and ethanol (600 ml) was added to the residue, followed by heating till a clear solution was obtained. The reaction mixture was gradually cooled with stirring, filtered and dried to provide triethylenetetramine dihydrochloride (1).

Yield: 88.9 g, (70 %)

Purity : $\geq$ 99%

Claims

1. A process for preparation of Trientine dihydrochloride (1) comprising reaction of tert-butyl-N-(2-aminoethyl)-N-2-[(2-aminoethyl)-(tert-butoxy)carbonyl]amino]ethyl} carbamate of formula (6) with hydrochloric acid to give Trientine dihydrochloride (1).
2. A process as claimed in claim 1, wherein the reaction is carried out in aqueous medium.
3. A process as claimed in claim 1, wherein the reaction temperature is maintained in the range of 80 to 110°C.
4. A process as claimed in claim 1, wherein the hydrochloric acid is used in the range of 1.6 to 2.1 molar equivalents..
5. A process as claimed in claim 1, wherein after completion, concentration of the reaction mass, further treatment with ethanol, followed by cooling and filtration yielded Trientine dihydrochloride (1).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/055439

A. CLASSIFICATION OF SUBJECT MATTER

C07C 209/44(2006.01)i; C07C 211/14(2006.01)n; C07C 209/00(2006.01)n

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C209; C07C211

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNABS,CNTXT,VEN,CNKI,CAPLUS: 三乙烯,四胺，二胺， 盐酸，曲恩汀，三亚乙基四胺，脱保护， 叔丁氧基，trientine, triethylenetetramine, diamine , dihydrochloride, Syprine, deprotection, t-butyloxy carbonyl，206531-21-7，38260-01-4

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006027705 A2 (PROTEMIX CORP LTD) 16 March 2006 (2006-03-16) Page 34，lines 1-20，23-24； Example11； Scheme11	1-5
PX	DISCLOSED Anonymously. "Process for preparation of Trientine hydrochloride" *IP.com Journal,* Vol. 16, No. 1A, 23 December 2015 (2015-12-23), ISSN: 1533-0001, pages 1-5	1-5
A	JP 2010105943 A (TOKUYAMA CORP) 13 May 2010 (2010-05-13) the whole document	1-5
A	CN 102924289 A (广东奥尔诚药业有限公司) 13 February 2013 (2013-02-13) the whole document	1-5

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 November 2016	**01 December 2016**

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2016/055439

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
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		EP 1778618 A2	02 May 2007
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