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Shiv Chhatrapati Shikshan Sanstha, Latur

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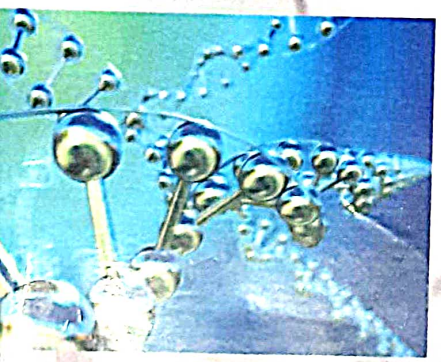

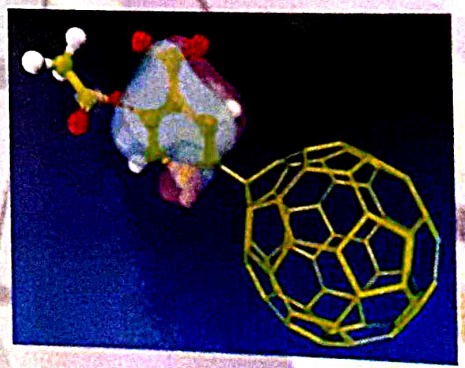

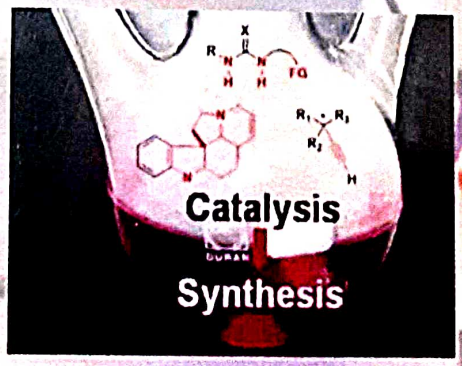

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Department of Chemistry And Analytical Chemist

CONTENTS

One-pot synthesis of pantoprazole sodium by reacting 2-chloro methyl 3, 4 - dimethoxy pyridine hydrochloride with 2-mercapto-5-difluoromethoxy benzimidazole

Rajkumar U. Pokalwar

Department of Chemistry, Degloor College Degloor, S. R.T. M. University,
Nanded- 431717 (M.S.) India.
E-mail: rajupokalwar@rediffmail.com

Abstract:

One-pot synthesis of pantoprazole sodium proton pump inhibitor by reacting 2-chloro methyl 3, 4 - dimethoxy pyridine hydrochloride with 2-mercapto-5-difluoromethoxy benzimidazole in methanol solvent in presence of sodium hydroxide base and further treating with aqueous sodium hypochlorite solution in presence of sodium hydroxide to obtain pantoprazole sodium in high yield and purity.

Keywords:

Pantpprazole sodium, Proton pump inhibitors, 2-chloro methyl 3, 4 - dimethoxy pyridine hydrochloride , 2-mercapto-5-difluoromethoxy benzimidazole, sodium hypochlorite.

Introduction:

Pantoprazole is a proton pump inhibitor drug that inhibits gastric acid secretion. Pantoprazole is used for short-term treatment of erosion and ulceration of the esophagus caused by gastroesophageal reflux disease. Pantoprazole may also be used in combination with antibiotics to treat ulcers caused by *Helicobacter pylori*. Pantoprazole was developed by Altana and was licensed in the USA to Wyeth. Similarly Omeprazole, Lansoprazole and Rabeprazole are antiulcer drugs in the class of proton pump inhibitors. For these all antiulcer drugs, Pyridine and 2-mercapto-1H-benzimidazole are the two key constituents of these drugs.

The derivatives of benzimidazole are possessed broad spectrum of biological activities including antibacterial, antiviral,[1] antitumor,[2] antimutagens,[3] cardiovascular,[4] anticalmodulin,[5] and many other activities are well documented.[6] In particular, mercapto benzimidazole is used for the synthesis of the most known prazole drugs pantoprazole,[7] omeprazole,[8] rabeprazole,[9] and lansoprazole[10] which are antiulcerous agents useful in the

treatment of stomach and duodenal ulcers. By all means, benzimidazole acts as "privileged substructure" for drug design. Among these, pantoprazole is the proton pump inhibitor drug used in gastroesophageal reflux disease and as antihelicobacter agent for the treatment of gastrointestinal disorders. Pyridine and 5-difluoromethoxy-2-mercapto-1H-benzimidazole are the two key constituents of this drug.

After the extensive literature search, it was observed that Pantoprazole was developed by Byk Gulden Lamberg Chemiche Fabrik GmbH and disclosed in U.S. Patent 4,758,579 and EP0166287. In one of the processes described in this patent application, 2-chloromethyl-3,4-dimethoxy pyridine was reacted with 2-mercapto-5-difluoromethoxy benzimidazole to prepare a precursor sulfide, which was isolated and oxidized by using metachloroperbenzoic acid to yield pantoprazole base. The prior art methods described above also involves the use of many hazardous reagents like hydrogen peroxide, metachloroperbenzoic acid, etc. Thus the processes from the prior art are unable to provide an environmentally safe and industrially applicable process with substantial yields.The main disadvantages of this process are formation of sulphone analogue which is difficult to remove, use of metachloroperoxybenzoic acid which is a costly reagent and that gives metachlorobenzoic acid as a byproduct thus increasing the impurity level.

The present invention has the advantage of simple reaction conditions, use of cheap and readily available reagents and solvents and efficient work-up procedure that leads to isolation of high purity product (purity above 99%). The present invention relates to a process for the preparation of pantoprazole sodium. More particularly, the invention relates to a one-pot process for the preparation of pantoprazole sodium in high yields and purity. Final products obtained in the present invention having almost negligible amount of sulfone impurity. More particularly it is an object of the present invention to provide viable and economically feasible process, thereby eliminating the above-mentioned shortcomings.

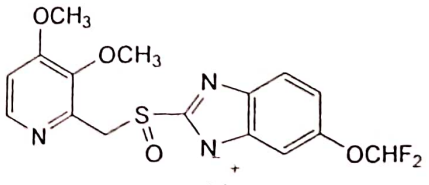
Result and Discussion:

The present invention discloses a novel one-pot process for the synthesis of pantoprazole sodium by reacting 2-chloro methyl 3, 4 -dimethoxy pyridine hydrochloride with 2-mercapto-5- difluoromethoxy benzimidazole in methanol solvent in presence of sodium hydroxide base and further treating with aqueous sodium hypohalite solution to obtain pantoprazole sodium in high yield and purity.

According to one aspect of the invention there is provided a process for preparation of pantoprazole sodium, comprising the steps of: (i) reacting 2-chloromethyl 3, 4 dimethoxy pyridine hydrochloride with 2-mercapto-5- difluoromethoxy benzimidazole in an organic solvent and aqueous sodium hydroxide solution in presence of a phase transfer catalyst to obtain pantoprazole sulphide; and (ii) treating said pantoprazole sulphide obtained in step (i) with an aqueous sodium hypohalite solution containing sodium hydroxide to yield pantoprazole sodium.

It is possible for the pantoprazole sulphide to be isolated between steps (i) and (ii). However, this is not preferred, as it is possible to improve the yield and purity of the pantoprazole sodium by taking the pantoprazole sulfide in the organic phase formed in step (i), and treating it with the hypohalite solution. Thus, in the preferred embodiment, there is no isolation of the pantoprazole sulphide between steps (i) and (ii). In the most preferred embodiment, the process is a one-pot process; this means that the steps (i) and (ii) are both carried out in the same reaction pot.

The present invention relates to a process for the synthesis of pantoprazole sodium of Formula I

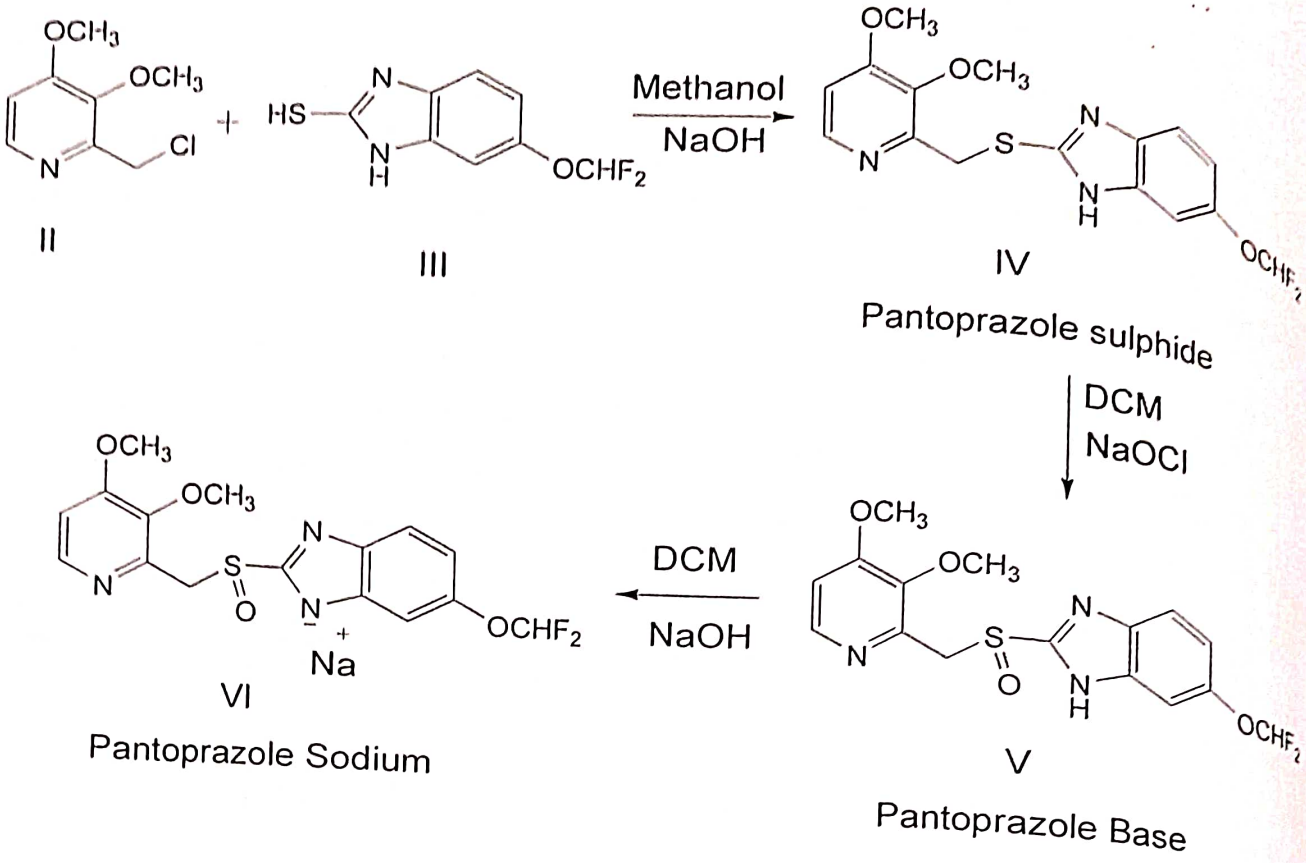


I

The present invention provides a process for the preparation of pantoprazole sodium wherein 2- chloromethyl-3,4-dimethoxypyridine hydrochloride (III) is reacted with 2-mercapto-5-difluoromethoxy benzimidazole (IV) in methanol solvent system and in presence of aqueous sodium hydroxide. This yields pantoprazole sulfide, which is converted to pantoprazole sodium without isolation of the sulfide. The temperature of the reaction preferably ranges from 25-35°C.

The process of the present invention is advantageously carried out in one pot without the isolation of any intermediates as illustrated in Scheme below.

Scheme:



The intermediates pantoprazole sulfide (IV) and pantoprazole base (V) as shown in the scheme were not isolated during the process of the present invention. In particular, they were not subjected to any purification. Further, the pantoprazole sulfide obtained in situ was oxidized using aqueous solution of sodium hypochlorite with a strength from 8- 10 %, and having the sodium hydroxide content is from 2.0 to 2.5 %. The oxidation of the pantoprazole sulfide is preferably carried out at a temperature ranging from 0^0-5°C. The pantoprazole sodium obtained by the process of the present invention has a very high level of purity and the known impurities like sulfone, sulfone N-oxide, and sulfide were below 0.15% and individual unknown impurities were less than 0.1% If peroxyacetic acid is used for the same purpose the sulfone impurity formation is 3 to 4% and with m-Chloroperoxybenzoic acid. sulfone formation in the reaction is also in the same range irrespective of temperature and other reaction conditions. To remove the sulfone analogue, the losses in repeated re-crystallization to bring it into pharmaceutically accepted limits is too high. Table shows the sulfone analogue formation using different oxidizing agents.

Sr. NO.	Oxidising agent used	% of Sulphone impurity formation
1.	Peroxyacetic acids	3 to 4 %
2.	m-chloroperbenzoic acid	3 to 5 %
3.	Sodium hypochlorite	NMT 0.5 %

Experimental Section:

Preparation of 5-(difluoromethoxy)-2[[(3,4-dimethoxy-2-pyridinyl) methyl]sulfinyl]-1H benzimidazole sodium:

2-Chloromethyl-3,4-dimethoxy pyridine hydrochloride (50 gm), 2-mercapto-5-difluoromethoxybenzimidazole (50 gm) under stirring to methanol (300 ml) followed by solution of sodium hydroxide (37.5 gm) in 120 ml water.The reaction mass stirred at 25 - 30° C for about 10 hours. After reaction completion, the methanol was evaporated then the aqueous layer was extracted with dichloromethane (300 ml) twice. The organic layers were combined together, water washed and distilled to about 300 ml and cooled to 0^0C. Added 20 ml 12 N NaOH solution and 8-10% aqueous sodium hypochlorite solution (150 ml) was added to the reaction mass, which was maintained at 0 - 5^0C for about 2-6 hours. After completion of reaction, reaction mass maintained for 1 hr at 0 - 5^0C. The resulting solid was then filtered and dried under vacuum at 35-40^0C to give pantoprazole sodium (78 gm, 85 % and HPLC purity 99 %).

Conclusion:

The present invention has the advantage of simple reaction conditions, use of cheap and readily available reagents and solvents and efficient work-up procedure that leads to isolation of high purity product (purity above 99%). The present invention relates to a process for the preparation of pantoprazole sodium. More particularly, the invention relates to a one-pot process for the preparation of pantoprazole sodium in high yields and purity. Final products obtained in the present invention having Formula I are almost negligible amount of sulfone impurity. More particularly it is an object of the present invention to provide viable and economically feasible process

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