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Novel process for the synthesis of Brimonidine and derivative

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Abstract: The novel method for synthesis of Brimonidine and it's derivative is described in this novel approach, 5-bromo-6-aminoquinaxaline and N-acetyl ethylene urea on condensation in presence of phosphorous oxychloride at temp 55-60°C gives 5-bromo-N-(1-acetyl-4,5-dihydro-imidazole-2-yl)-6-quinoxalanamine (acetyl brimonidine), which on hydrolysis with methanolic sodium hydroxide gives 5-bromo-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)-6-quinoxalin-6-amine (Brimonidine) and which on treatment with tartaric acid in methanol gives Brimonidine tartrate.
Keywords: 5-bromo-6-aminoquinaxaline, N-acetyl ethylene, 5-bromo-N-(1-acetyl-4,5-dihydro-imidazole-2-yl)-6-quinoxalnamine, 5-bromo-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)-6-quinoxalin-6-amine, acetyl brimonidine, Brimonidine, Brimonidine tartrate.

Introduction

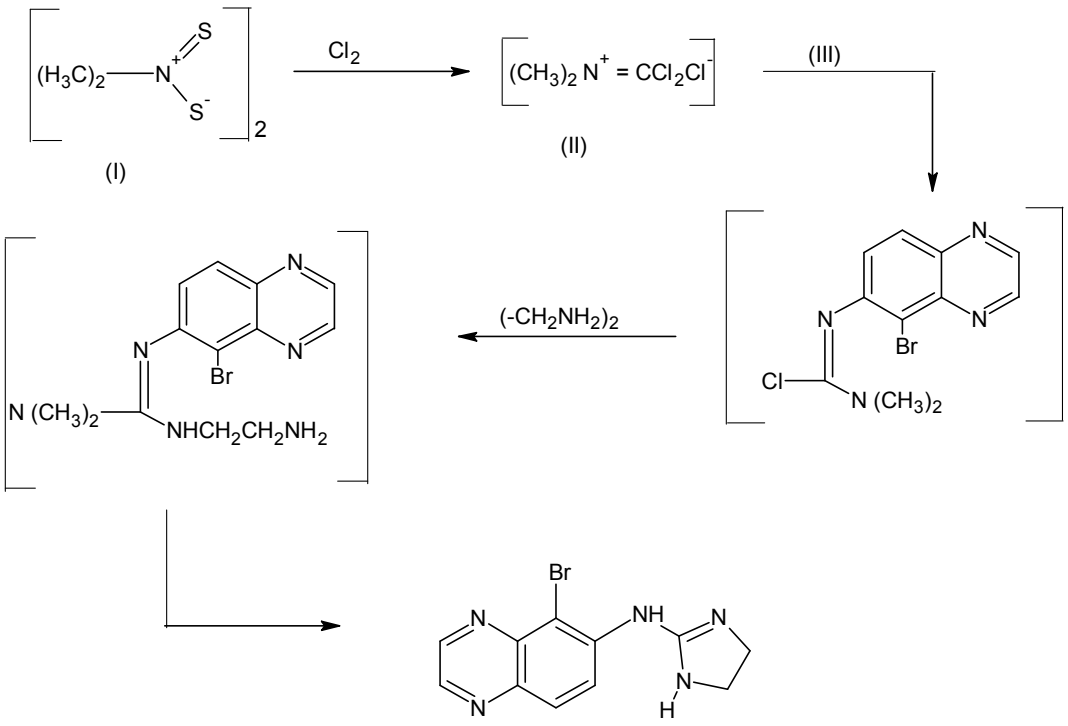
Brimonidine is a drug used in treatment of open-angle glaucoma or ocular hypertension [1]. It is also used to induce miosis for people suffering from poor night vision after Lasik or PRK surgery [2]. It acts via decreasing synthesis of aqueous humor, and increasing the amount that drains from the eye. As a treatment for glaucoma, it is usually given in the form eyedrop of Brimonidine as an α_2-adrenergic receptor agonist.Alpha 2 agonists, through the activation of the Gi GPCR, inhibit the production of AC. This reduces cAMP and hence Aqueous Humour production by the ciliary body [3].

Several approaches has been disclosed in various published patents for the synthesis of Brimonidine and its derivatives, Some of relevant patents are US 3890319, US 5021416, US6323204, RU 2285003, US 5130441, GB 1463520.

Process of synthesis of Brimonidine as given in US 3890319 involves the use of benzene which is carcinogenic and hence prohibited by all health agencies worldwide. Moreover this process involves the use of thiophosgene and evolves toxic hydrogen sulphide gas, which is highly dangerous on commercial scale.

Column separation technique is referred in US 6323204, which is not viable on commercial scale. Also, involve the use of thiophosgene gas in the process Leads to evolution of hydrogen sulphide gas.

In Russian patent no. RU-2285003, Brimonidine base was prepared by reaction of immonium chloride (II)[prepared by chlorination of tetramethyl thioperoxydicarbonic diamide in CH_2Cl_2 at 20 ºC] with 6-amino -5-bromo quinoxaline (III) at reflux for 1 hour followed by reaction with 1,2 ethanediamine at 20 ºC for 2 hrs. with 38.4% yield.



In above patent preparation, yield is very inferior and the number operations are more in numbers which is undesired for large scale preparation.

Other process disclosed in US 5130441, in which Brimonidine was prepared by reacting 6-amino-5-bromo quinoxaline and imidazoline 2- sulphonic acid in isobutanol at 125 ºC for 16 hours to obtain a 5-bromo 6-(2-imidazoline -2 yl amino) -quinoxaline which is purified by column chromatography to obtain pure Brimonidine base .

In above patent brimonidine base isolated by column chromatography which is a tedious, costly and time consuming process for scale up preparation. Furthermore a imidazoline -2- sulphonic acid is not commercially available and also use of MoO (molybdenum oxide) and immersion cooler for the preparation, which is not feasible for the large quantity .

As referred to patent GB-1463520**,** 6-amino-5- bromo quinoxaline in acetone treated with benzoyl chloride and ammonium thiocynate to obtain 5- bromo-6-thiouredo quinoxaline furthermore treated with bromobenzene and ethylenediamine to get Brimonidine.

In this preparation the major disadvantage is, the number of operations required for the preparation of title compound and considering the cost and utility point of view is very tedious and time consuming. In this process hydrogen sulphide librated in final stage which is toxic in a large scale preparation and use large volume of bromobenzene at temperature 150-155 ºC.

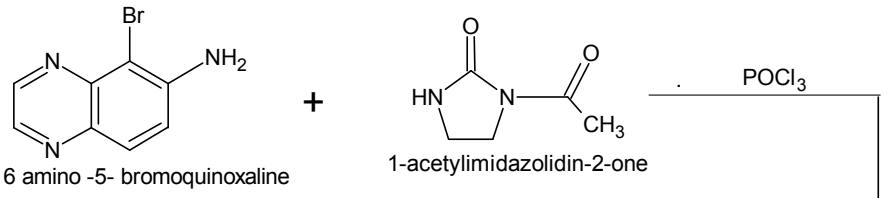
All above described processes has serious drawbacks like use of carcinogenic solvent , evolution of toxic gas, use of column chromatography for separation , long reaction time and high reaction temperature.
Our process is directed to the novel, industrially applicable and commercially feasible process for the preparation of brimonidine. The invented process is carried out under mild condition and without isolation of intermediate substance and without use of highly toxic reagent with good yield and purity.

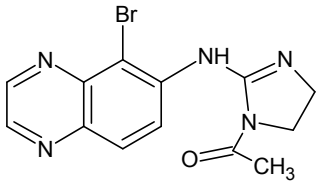
Our new process involves,
In step I, N-acetyl ethylene urea and 6-amino-5- bromo quanoxaline are reacted in presence of phosphorus oxychloride at 55-60 ºC to forms N-acetyl brimonidine. In step II, acetyl brimonidine hydrolyzed in methanolic sodium hydroxide to form brimonidine base which on reaction with tartaric acid in methanol gives brimonidine tartrate in good yield and purity.
This is a novel method of preparation of brimonidine and its salt with environment friendly process which described below.

Novel synthetic approach of Brimonidine:

The novel method for the preparation of brimonidine involves following steps.

Step-I



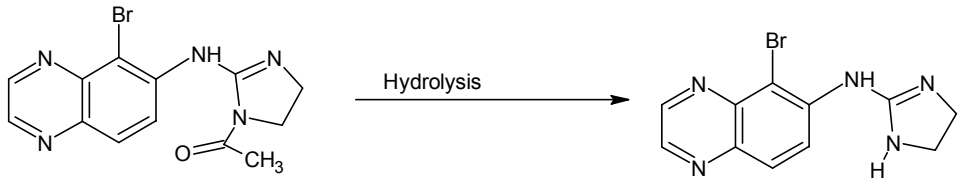


5- bromo-N-(1-acetyl-4,5 -dihydro-imidazole-2-yl)-6 -quinoxaline

In step–I of the preparation of acetyl brimonidine, in which condensation of 6-amino-5- bromoquinoxaline (0.22 mole) and N- acetyl ethylene urea (0.41mole) are reacted in presence of phosphorus oxychloride (4.27 mole) at 55-60 ºC for 40 hours.

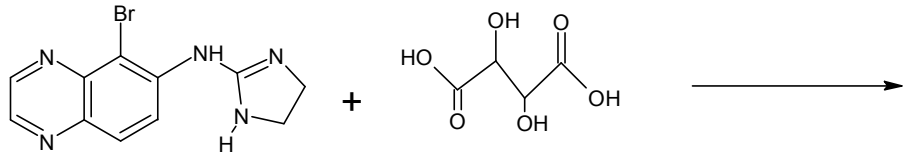
After completion of reaction excess phosphorus oxychloride distilled out under vacuum and reaction mass was diluted with organic solvent such as methylene dichloride, ethylene dichloride or toluene reaction mass was further cooled to ambient temperature and further 15-20 ºC, the ice cold water was added to reaction mass and further stirred for 8 hours to ensure the complete decomposition of phosphorous oxychloride . The sodium hydroxide solution was added in reaction mixture till pH 8-9 .The solid precipitated were filtered and suck dried to obtained acetyl brimonidine.

Step –II:

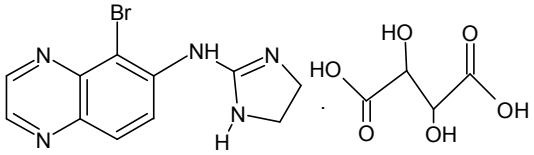


5- bromo-N-(1-acetyl-4,5 -dihydro-imidazole-2-yl)-6 -quinoxaline

5- bromo-N-(4,5 -dihydro-imidazole-2-yl)-6 -quinoxaline



5- bromo-N-(4,5 -dihydro-imidazole-2-yl)-6 -quinoxaline tartaric acid



Brimonidine Tartrate

In Step –II, acetyl brimonidine obtained in step –I is hydrolyzed with methanolic sodium hydroxide to obtain a brimonidine base.
The brimonidine base obtained from the above step is converted to brimonidine tartrate by reacting it with tartaric acid in methanol.

Experimental
In 1 lit RB flask Charged phosphorus oxychloride (400 ml) and 6-amino -5-bromo quinoxaline (50 gms) at ambient temperature followed by N-acetyl ethylene urea (53 gms) in two lots and the reaction mixture was stirred at room temperature for 15 min. Further the reaction mixture heated to 55-60^{o}C and maintained for 40 hrs. At the end of the reaction (as indicated by TLC), phosphorus oxychloride was distilled out under vacuum at 55-60^{o}C. The reaction mass was diluted with organic solvent such methylene dichloride, ethylene dichloride or toluene, cooled to room temperature and further to 15-20^{o}C. Ice-cold water (250 ml) was added to the reaction mixture at temperature below 20^{o}C and the reaction mass was stirred for 8 hrs. Sodium hydroxide solution was added till pH 8-9. The solids precipitated were filtered and suck dried. Acetyl brimonidine (28 gms) thus obtained was hydrolyzed in methanolic sodium hydroxide. The free base thus obtained (22.2 gms) was converted to tartrate salt by reacting it with tartaric acid in methanol.

Analytical results and interpretation: The compound (Brimonidine tartrate) synthesized by above described novel process is interpreted by analytical data given herewith.m.p.: 208°C, IR (medium, cm^{-1}) 1917 (=C=O stretching), 1730 (CH stretching), 1485 (CH stretching), 1298 (CH stretching), 1215 (CH bending), 1077 (CH bending) 1730 (CH stretching),, ^{1}H NMR ppm : 9.2 (m, 4H), 8.9 (s, 1H), 8.8 (s, 1H), 7.95 (d, 1H), 7.7 (d, 1H), 7.1 (s, 2H), 3.5 (s, 4H), 4.19 (s, 2H), Mass: corresponding peaks obtained at 291.7, 293.8, 21.1, 213.2, 83, 71, 131, 74, Elemental analysis: C:41.07%, H: 4.14%, N: 15.85%, Br: 18%, O:20%.

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4. Patents US 3890319, US 5021416, US6323204, GB 1463520, US 5130441, RU 2285003

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