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AN EFFICIENT AND NOVEL PROCESS FOR THE SYNTHESIS OF NIZATIDINE

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Abstract: A facile echo friendly, cost effective and robust process for the synthesis of Nizatidine *via* the cyclocondensation of 2-(dimethylamino) ethanethioamide with ethyl bromopyruvate followed by reduction then coupled with cysteamine hydrochloride. The later formed product was coupled with (*N*-methyl-1-(methylthio)-2-nitroethenamine in water resulted Nizatidine. The synthesized product was meet European pharmacopeia (*EP*) monograph.

Keywords: Ethyl bromopyruvate, 2-(dimethylamino) ethanethioamide, K_2CO_3,Cysteamine hydrochloride, $NaBH_4$ and*N*-methyl-1-(methylthio)-2-nitroethenamine.

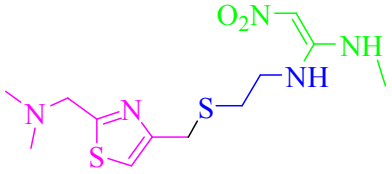
Introduction

Thiazoles are of eminent importance because of their potential as bioactive Compounds[I &II]and versatile building blocks for natural products and pharmaceuticals[III& IV]. Thiazoles are important class of heterocyclic compounds and are found to exhibit various pharmacological activities namely anti-inflammatory, antimicrobial, [V&VI] antitumor, [VII] anticonvulsant, [VIII] analgesic,[IX] and anticancer agents[X].

Nizatidine (**I**) is an oral histamine H_2-receptor antagonist similar to Cimetidine, Famotidine and Ranitidine. Nizatidine (**I**) inhibits stomach acid production, and commonly used in the treatment of peptic ulcer disease (PUD) and gastro esophageal reflux disease (GERD).

Nizatidine (**I**) was developed by Eli Lilly, and was first marketed in 1987. It is considered to be equipotent with ranitidine and differs by the substitution of a thiazole ring in place of the furan ring in ranitidine.Nizatidine (**I**) proved to be the last new histamine H_2 receptor antagonist introduced prior to the advent of proton pump inhibitors.

Nizatidine (**I**), the systematic chemical name of which *N*-2-([2-(dimethylaminomethyl)-5-methyl-4-thiazolyl]methylthio)ethyl-*N'*-methyl-2-nitro-1,1-ethenediamine, having the structure (**I**).This compound is a histamine H_2-receptor antagonist which is useful as anti-ulcer agents capable of inmbiting gastric acid secretion in mammals.



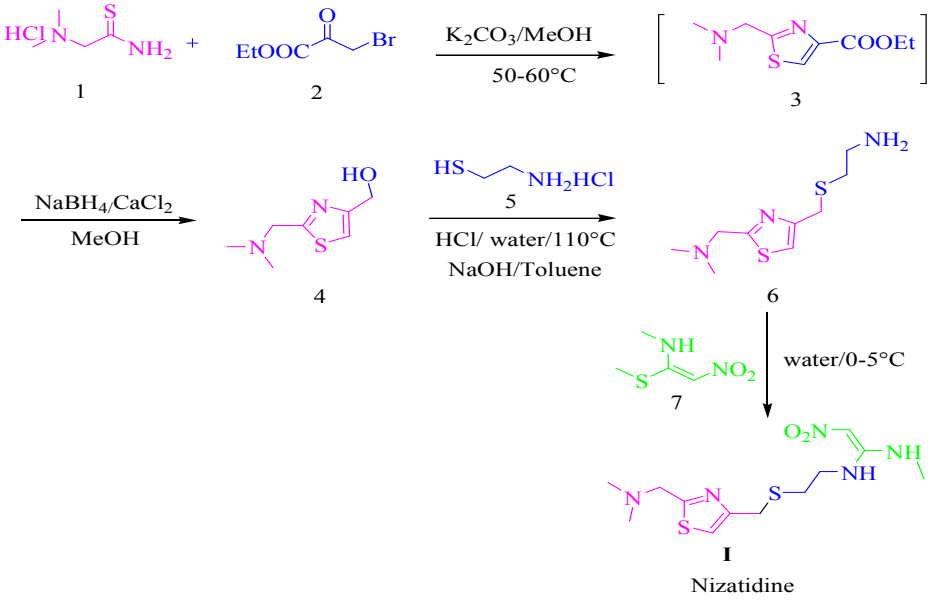
I

Nizatidine

Hartford W. Manning reportedcyclization of 2-(Dimethylamino)thioacetamide hydrochloride(**1**)with ethyl bromopyruvate (**2**)in refluxing ethanol gives ethyl 2-(dimethylaminomethyl)-4-thiazolecarboxylate (**3**), which is reduced with lithium triethyl borohydride in THF yielding 2-(dimethylaminomethyl)-4-thiazolemethanol (**4**). The condensation of (**4**) with 2-aminoethanethiol (**5**) by means of 48% HBr affords 2-(dimethylaminomethyl)-4-(2-aminoethylthiomethyl)thiazole (**6**), which is finally condensed with 1-(methylthio)-2-nitro-*N*-methylethyleneamine (**7**) in water resulted Nizatidine (**I**) [XI].

Results and Discussion

The present work describes the design and synthesis of Nizatidine drug substance by using less expensive, eco-friendly reagents and cost-effective way. Mainly 2-(Dimethylamino)thioacetamide hydrochloride (**1**) is condensed with ethyl 3-bromo-2-oxopropanoate (**2**) in presence of methanol gives ethyl 2-(dimethylaminomethyl)-4-thiazolecarboxylate (**3**), which ester group is reduced by using $NaBH_4$ & $CaCl_2$ resulted corresponding alcohol (**4**), the later one chlorination by using aqueous HCl resulted chloro compound*in-situ*. This chloro compound coupled with 2-aminoethanethiol (**5**) to form 2-(dimethylaminomethyl)-4-(2-aminoethylthiomethyl) thiazole (**6**), which is condensed with 1-(methylthio)-2-nitro-*N*-methylethyleneamine (**7**) in water resulted Nizatidine (**I**) as shown in **Scheme-1**



Scheme-1

Conclusion

The developed process is a robust, echo friendly and cost-effective method for the synthesis of Nizatidine from *in-situ* way. Also, the required key starting materials are commercially available. This newly established route of synthesis of Nizatidine getting good yield &quality and useful for the commercial scale.

Experimental Section

General Methods

All reactions were carried out in oven-dried glassware (120 °C) under an atmosphere of nitrogen unless as indicated otherwise. Melting points were determined on a Polmon instrument (model no. MP 96).IR spectra were recorded on FT-IR Perkin-Elmer 1605 spectrometer and ^{1}H NMR (400 MHz) and ^{13}C NMR (400.6 MHz) were recorded on a Varian Gemini 200 spectrometer using TMS as internal standard (chemical shifts and *ppm*). UV spectra were obtained on a Shimadzu UV-visible spectrophotometer (model UV-1601). Mass spectra were recorded on a VG micromass70-70H instrument.

Synthesis of Ethyl 2-(Dimethylaminomethyl)-4-thiazolecarboxylate (3)

A reaction mixture was prepared containing 15.5g (0.10mol) of 2-dimethylaminothioacetamidehydrochloride(**1**), 21.5g (0.11mol) of ethyl bromopyruvate (**2**) and 20.76g (0.15mol) of potassium carbonate in 150 ml of methanol. The reaction mixture was heated to reflux temperature for about 4 hours. Aftercompletion of reaction then reaction mass cooled to room temperature, un-dissolved salts were filtered by normal filtration and the filtrate containing ethyl 2-(dimethylaminomethyl)-4-thiazolecarboxylate (**3**) proceeded to*in-situ* for next reaction.

Synthesis of 2-(Dimethylaminomethyl)-4-thiazolemethanol (4)

A solution of 21.5 g (0.10 mol) of ethyl 2-(dimethylaminomethyl)-4-thiazolecarboxylate(**3**) cooled to about 0°C under nitrogen atmosphere and charged 13.36 g (0.12 mol) of $CaCl_2$. To this mixture slowly charged 4.17 g (0.11mol) of sodium borohydride in portion wise at below 5°C. Then reaction mixture allowed to heat up to ambient temperature and maintained for 2 to3 hrs. Reaction progress was monitored by TLC and the un-reacted (**3**) was less than 1%. Un-dissolved salts were filtered off and salts were washed with 20 ml of methanol and combined methanol layer concentrated under vacuum. The residue consisting of brown oil weighing about 15.0 g comprised 2-(dimethylaminomethyl)-4-thiazolemethanol (**4**) formed (yield; **87**%).

^{1}HNMR (DMSO-d_6, 400 MHz): δ 7.32 (s, 1H), 5.27 (d, 1H, J = 4.8 Hz), 4.51 (d, 2H, J = 4.4 Hz), 3.69 (s, 2H), 2.25 (s, 6H, $N(CH_3)_2$),;

^{13}C NMR (DMSO-d_6, 400 MHz): δ 170.05, 157.1, 114.7, 60.3, 59.7, 45.1,;

MS:*m/z* calculated 172.07 and observed *m/z* 173.1$[M+H]^+$,;

Synthesis of 2-([2-(Dimethylaminomethyl)-4-thiazolyl)] methylthio) ethylamine (6)

A reaction mixture was prepared from 15 g (0.087mol) of 2-dimethylaminomethyl-4-thiazolemethanol (**4**), 10.39 g (0.0827mol) of 2-aminoethanethiol hydrochloride (Cysteamine hydrochloride) (**5**) and 25 ml (0.2175 mol) of 33% concentrated hydrochloric acid. The reaction mixture was stirred at about 110° C for about 12 hours. Reaction mixture cooled to below room temperature and basified with caustic soda solution to above *pH*is 10.5 and compound extracted with 5x25 mL of toluene. Organic layer concentrated under vacuum. The resultant reddish brown oil to yield 16.2 g comprising 2-([2-(methylaminomethyl)-4-thiazolyl] methylthio) ethylamine (**6**) (yield: 80%).

The compound had the following physical characteristics:
^{1}HNMR (DMSO-d_6, 400 MHz): δ 7.39 (s, 1H), 3.78-3.70 (d, 4H, *J* = 6.4 Hz), 2.71 (t, 2H), 2.47 (m, 4H), 2.25 (s, 6H, $N(CH_3)_2$),;
MS:*m/z* calculated 231.09 and observed *m/z* 232.1$[M+H]^+$,;

Synthesis of *N*-2-([2-(dimethylaminomethyl)-5-methyl-4-thiazolyl] methylthio) ethyl-*N′*-methyl-2-nitro-1, 1-ethenediamine (Nizatidine) (I)

A stirred solution of 15 g (0.0648 mol) of 2-([2-(dimethylaminomethyl)-5-methyl-4-thiazolyl] methylthio) ethylamine (**6**) taken in to 60 mL of water and treated with 9.5 g (0.0641 mol) of *N*-methyl-1-methylthio-2-nitroethyleneamine (**7**). The reaction mixture was kept under stirring at 0-5°C overnight. The reaction mixture slowly heated up to room temperature and extracted with dichloromethane (3x25 mL) and the organic layer washed with water followed by concentrated by evaporation of the dichloromethane and the resulting yellow residue was triturated with methanol providing an light yellow solids yielded 15 gm of *N*-2-([2-(dimethylaminomethyl)-5-methyl-4-thiazolyl]methylthio) ethyl-*N′*-methyl-2-nitro-1, 1-ethenediamine crude(**I**). Obtained solids were re-crystallization in methanol resulted in 17.18 g off white solid of pure Nizatidine (**I**).

Melting point: 130-132° C
Yield: 80 %.
^{1}HNMR (DMSO-d_6, 400 MHz): δ 10.04 (bs, 1H), 7.42 (s, 1H), 7.22 (d,1H), 6.44(d, 1H), 3.84 (s, 4H), 3.71 (m, 2H), 2.84-2.69 (m, 5H), 2.25 (s, 6H, $N(CH_3)_2$),;
MS:*m/z* calculated 331.1 and observed *m/z* 332.1$[M+H]^+$,;

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