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Technical Notes

An Improved Synthesis of Antiulcerative Drug: Tenatoprazole

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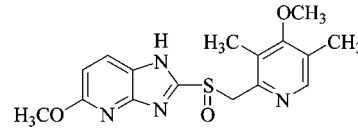
Abstract:

An efficient, cost-effective and multikilogram-scale process for the synthesis of tenatoprazole 1, an antiulcerative drug, is described. The key steps in this synthesis involve the coupling of 2-mercapto-5-methoxyimidazo[4,5-*b*]pyridine 2 with 2-chloromethyl-4-methoxy-3,5-dimethyl pyridine hydrochloride 3 to yield 4 and its subsequent oxidation with *m*-CPBA to produce sulfoxide 1. The process has been scaled up for the multikilogram-scale of compound 1 with an overall yield of 72%. The new process requires no purification process and affords the target compound 1 with 99.8% purity by HPLC.

Introduction

Tenatoprazole is a novel imidazopyridine derivative and has an imidazopyridine ring in place of the benzimidazole moiety found in other proton pump inhibitors.[1] It is activated more slowly than other proton pump inhibitor, but its inhibition is resistant to reversal.[2] Tenatoprazole has an extended plasma half-life in comparison with those of all other proton pump inhibitors; this makes it more potent in the treatment of nocturnal acid breakthrough than esomeprazole, one of the most popular proton pump inhibitors.[3,4]

Tenatoprazole belongs to the class of covalent proton pump inhibitors (PPIs), which is converted to the active sulfenamide or sulfenic acid by acid in the secretory canaliculus of the stimulated parietal cell of the stomach.[5,6] This active species binds to luminally accessible cysteines of the gastric H^+,K^+-ATPase, resulting in disulfide formation and acid secretion inhibition.[7,8] Tenatoprazole binds at the catalytic subunit of the gastric acid pump with a stoichiometry of 2.6 nmol mg^{-1} of the enzyme in vitro. In vivo, maximum binding of tenatoprazole was 2.9 nmol mg^{-1} of the enzyme at 2 h after intravenous (IV) administration.[9,10]



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As outlined in Scheme 1, the existing process of tenatoprazole **1** involves two steps.[11] Synthesis of target compound **1** commences with the coupling of 2-mercapto-5-methoxyimidazo[4,5-*b*]pyridine **2** with 2-chloromethyl-4-methoxy-3,5-dimethyl pyridine hydrochloride **3** in the presence of potassium hydroxide affords **4** with 73% yield in ethanol and chloroform. Although this condensation reaction was very good, it requires high solvent volumes for the reaction, which was not a better choice at large-scale production. The oxidation of the penultimate sulfide intermediate **4** with *m*-CPBA in chloroform (100 vol) afforded **1** in moderate yields with the potential impurities such as sulfone **6**, *N*-oxide **7**, sulfone *N*-oxide **8**, and sulfide **4**. Removal of these impurities from the product is very difficult. By keeping these compelling factors we thought to develop an improved process, which could circumvent most of the above-mentioned problems.

Results and Discussion

In our development efforts we needed to set up an efficient process for the impurity-free synthesis of tenatoprazole, **1**. The

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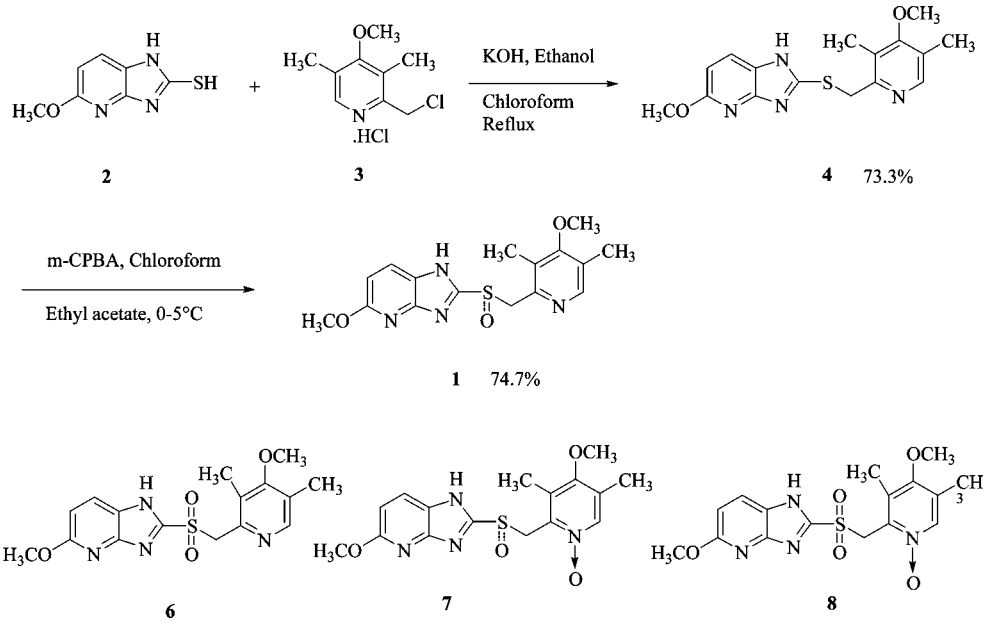
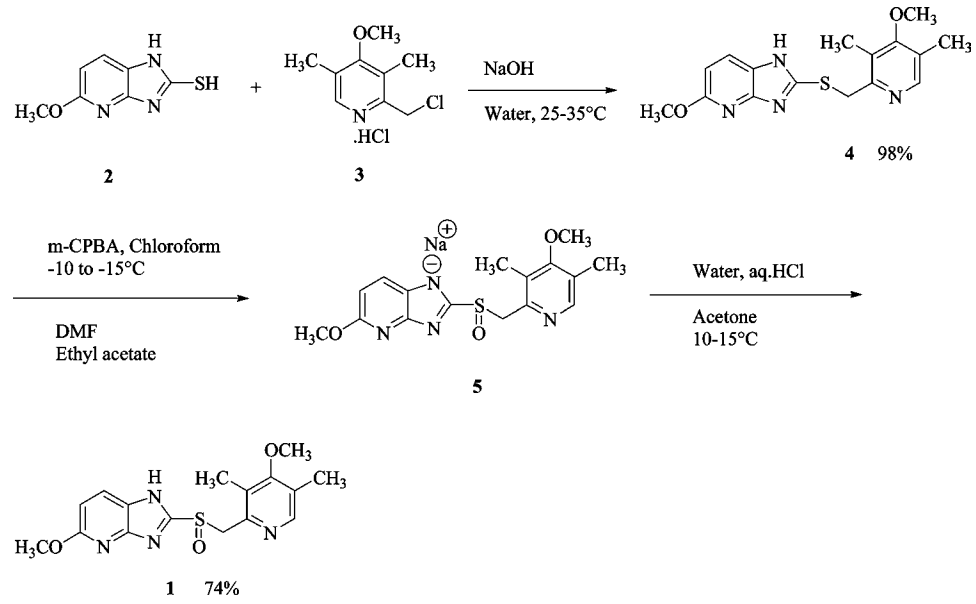
Scheme 1. **Existing process**



Scheme 2. **New process**



first task of our project was to remove the organic solvents in the condensation step. At the same time it was imperative to choose the reaction conditions in such a way that would allow scaling up of the procedure. As described in Scheme 2, the synthesis of **1** begins with the solvent-free condensation of 2-mercapto-5-methoxyimidazo[4,5-*b*]pyridine **2** with 2-chloromethyl-4-methoxy-3,5-dimethyl pyridine hydrochloride **3** to deliver the sulfide intermediate **4** with 98% yield. In this particular reaction we succeeded in obtaining the condensed sulfide with high yield and purity under solvent-free conditions. The patent route for this reaction requires reflux temperature and a large volume of ethanol (55 vol) and chloroform (276 vol). The yield of this reaction was dramatically increased from 73% to 98% by using our eco-friendly reaction conditions.

The final and important step of the synthesis is the oxidation of the sulfide intermediate with *m*-CPBA to form tenatoprazole **1**. The sulfide intermediate **4** on treatment with 0.9 equiv of *m*-chloroperbenzoic acid (*m*-CPBA) at −10 to −15 °C afforded the crude tenatoprazole which was isolated as its sodium salt. The sodium salt of tenatoprazole **5** was purified by recrystallsation using dimethyl formamide and ethyl acetate (2:1 ratio) to yield the pure crystalline tenatoprazole sodium **5**. Treatment of tenatoprazole sodium **5** with dil. HCl in the presence of acetone and water afforded the pure tenatoprazole **1** with 99.8% purity by HPLC. Although we have reduced only the solvent volumes in this oxidation step, our process is more practical and effective because it gives the impurity-free synthesis of tenatoprazole **1**.

The advantages of our process 2 over the product patent route as presented in Scheme 1 consist of the following: (i) Solvents were removed, and the yield was improved by 25% in the preparation of sulfide **4**. (ii) Chloroform volume was reduced from 100 to 15 volumes in the oxidation step. (iii) The

overall yield was increased from 55% to 72% with very good quality.

In conclusion, we have developed and described an improved and efficient process for the synthesis of tenatoprazole **1**, which offers distinctive advantages over the published procedure and significant cost reduction on commercial scale. This process is amenable for the large-scale production of tenatoprazole **1**.

Experimental Section

The ^{1}H and ^{13}C spectra were recorded in DMSO at 200 MHz on a Varian Gemini 200 MHz FT NMR spectrometer. The chemical shifts were reported in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state as KBr dispersion using a Perkin-Elmer 1650 FT-IR spectrophotometer. The mass spectrum (70 eV) was recorded on a HP-5989a LC/MS spectrometer. The melting points were determined by using the capillary method on a POLMON (model MP-96) melting point apparatus. The solvents and reagents were used without any purification.

Preparation of 2-[2-(3,5-Dimethyl)pyridylmethylthio]-5-methoxyimidazo[4,5-*b*]pyridine 4. To a solution of 2-mercapto-5-methoxyimidazo[4,5-*b*]pyridine (**2,** 20 kg, 0.11 mol), sodium hydroxide (9.72 kg, 0.24 mol), in water (160 L) was added a solution of 2-chloromethyl-4-methoxy-3,5-dimethyl pyridine hydrochloride (**3**, 27 kg, 0.12 mol), in water (100 L) at 25−30 °C over a period of 30−45 min. The reaction mixture was stirred for 2−3 h. After completion of the reaction (TLC), the isolated solid was filtered, washed with water (40 L), and dried at 60−70 °C under vacuum to afford 2-[2-(3,5-dimethyl)pyridylmethylthio]-5-methoxyimidazo[4,5-*b*]pyridine (**4**, 35.7 kg, 98%). Purity by HPLC 98.5%; ^{1}H NMR (200 MHz, DMSO) δ 2.2 (s, 6H), 3.7 (s, 3H), 3.9 (s, 3H), 4.3 (s, 2H), 6.6 (d, 1H), 7.7 (d, 1H), 8.3 (s, 1H), 12.8 (s, 1H).

Preparation of 2-[2-(3,5-Dimethyl)pyridylmethylsulfinyl]-5-methoxyimidazo[4,5-*b*]pyridine 1. To a stirred mixture of 2-[2-(3,5-dimethyl)pyridylmethylthio]-5-methoxyimidazo[4,5-*b*]pyridine (**4**, 20 kg, 0.06 mol) in chloroform (200 L) was added a solution of *m*-CPBA (9.4 kg, 0.05 mol) in chloroform (100 L) at −10 to −15 °C over a period of 45−60 min. The reaction mixture was stirred for 30−45 min at the same temperature. After completion of the reaction (TLC), the reaction mixture was poured into a solution of sodium hydroxide (14 kg, 0.35 mol) in water (140 L) and stirred for 1−2 h at 10−15 °C. The separated solid was filtered and washed with chloroform (60 L), suck dried for 45−60 min. A mixture of the wet cake above and dimethyl formamide (100 L) was heated to 65−70 °C to get a clear solution. The solution was cooled to 25−35 °C, and ethyl acetate (50 L) was added and stirred for 3−4 h. The isolated solid **5** was filtered and washed with ethyl acetate (10 L), vacuum dried for 45−60 min. To the above wet cake a mixture of water (50 L) and acetone (25 L) was added, the pH was adjusted to 7.5−8.0 using aq HCl (∼18 L) at 10−15 °C and stirred for 30−45 min. The solid was filtered and washed with water (6 L), dried at 45−50 °C under vacuum to afford 2-[2-(3,5-dimethyl)pyridylmethylsulfinyl]-5-methoxyimidazo[4,5-*b*]pyridine (**1**, 15.5 kg, 74%). Purity by HPLC 99.8%; ^{1}H NMR (200 MHz, DMSO) δ 2.2 (s, 6H), 3.8 (s, 6H), 4.8 (s, 2H), 6.6 (d, 1H), 7.8 (d, 1H), 8.2 (s, 1H), 13.0 (s, 1H).

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