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Communications to the Editor

An Improved and Single-Pot Process for the Production of Pantoprazole Substantially Free from Sulfone Impurity

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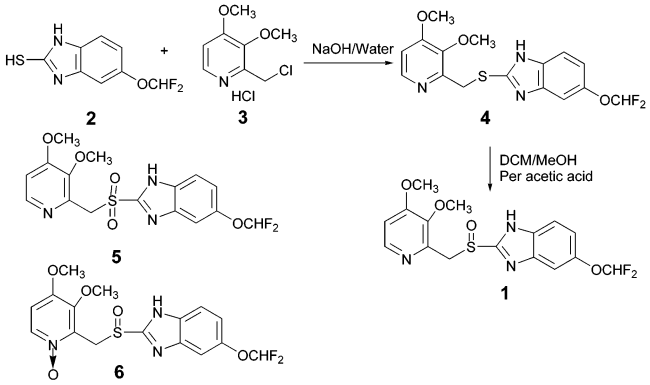
Abstract:

Pantoprazole (1), a substituted benzimidazole derivative, is an irreversible proton pump inhibitor, essentially used for the prevention and treatment of gastric acid-related diseases. The process for its preparation generally suffers from the drawback of producing a potential sulfone impurity (5). The present work details a report of the journey towards the development of a simple, single-pot process for the production of pantoprazole, substantially free from sulfone impurity (5). The detailed study of the different parameters affecting the purity and yield of the compound has been presented.

Pantoprazole (**1**) is an oral, pharmaceutically active compound having promising anti-ulcer activity[1] and belongs to the class of 2-[[(2-pyridinyl)methyl]sulfinyl]-1H-benzimidazoles. In general this class are used for the prevention and treatment of gastric acid-related diseases.[2] Literature studies reveal different methods for the preparation of pantoprazole.[3] The general process for the preparation[2] of pantoprazole involves condensation of thiol derivative **2** with chloromethyl pyridine derivative **3** in the presence of inorganic base to yield 5-(difloromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio-1H-benzimidazole (**4**), which upon further oxidation with a suitable oxidizing agent leads to the desired pantoprazole (**1**) as shown in Scheme 1.

The most important and critical step in the process is the oxidation wherein there are chances of formation of two impurities viz., pantoprazole *N*-oxide (**6**) and pantoprazole sulfone (**5**) as these are mentioned in the recently published analytical drug profile.[4] The former is formed due to the oxidation at the nitrogen center of the pyridine moiety, and

Scheme 1



the later is generated due to the over-oxidation of the sulfoxide derivative (**1**). However the *N*-oxide impurity was observed always in the range from 0.02 to 0.05% in the lab experimental studies, whereas sulfone was seen as a potential impurity. Due to similarity of the sulfone compound structure with that of the parent compound, complete removal of **5** proved problematic.

Different oxidizing agents[5] such as peracids, peresters, and peroxides were employed for the conversion of the sulfide derivative (**4**) to the sulfoxide derivative (**1**); preferred conditions mentioned in the literature included oxidizing the sulfide derivative (**4**) with an approximately equimolar quantity of the oxidizing agent in an organic solvent. The most recent version[6] of the process involved the oxidation of **4** using *tert*-butyl hydroperoxide and $VO(acac)_4$. Yet another version[7] involved oxidation of **4** with *m*-chloroperoxy benzoic acid followed by successive pH adjustments to yield pantoprazole in the organic layer. Concentration of the organic solvent followed by crystallization in acetone resulted in the formation of fine solid crystals. All the processes described previously suffered from the drawback of producing a considerable amount of **5**. Also, a second major drawback in many of the previous processes was the usage of heavy metal reagents, such as vanadium, which may prove

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Table 1. **Measured solubilities of 1, 5, and 4**

	solvents[a]				pH[b] (acetonitrile−water)					
cmpd	MeOH	IPA	ACN	$CHCl_3$	9.0	9.2	9.5	9.8	10.5	11.5
1	+++	+	++	+++	−	−	−	−	+	+
5	+++	+	++++	+++	−	+	+	+	+	+
4	++++	+	++	++++	−	−	−	−	−	−

[a] Notations used in case of solvents: + = very slightly soluble, ++ = slightly soluble, +++ = sparingly soluble, and ++++ = soluble. [b] Notations used incase of pH: + = soluble, and − = insoluble.

difficult to remove. No other relevant references disclosed pantoprazole with sulfone impurity less than 0.10%. Hence, there has been a need for an efficient, impurity-free, robust, and plant-friendly process for the preparation of pantoprazole and its pharmaceutically acceptable salts.

The optimization of the various parameters involved in the oxidation step resulted in a dramatic improvement in the purity of the compound. The workup further involved the exploitation of a fine difference in the solubility of the sodium salts of sulfone and sulfoxide at a given pH range in a solvent system. The measured solubilities of compounds **1**, **4**, and **5** in different solvents and different pH are given in Table 1.

The pure form of the sulfoxide **1** (containing sulfone impurity **5** less than 0.05%) is precipitated as a fine solid by adjusting the pH of reaction mixture to a specific range of 9.3−9.7. The sulfone impurity **5** is left behind in the mother liquor in the form of sodium salt, and it is thus easily removed during the filtration. Described below is an improved and single-pot approach for the synthesis of **1** with exceptionally high purity. The present process is a result of the optimization of the various parameters involved in the reaction as well as the workup. The process is highly efficient in consistently producing good-quality product. The percentage of the sulfone impurity **5** obtained in this process was always less than 0.1% in the worst case, and it was observed to be less than 0.05% in the production samples.

In addition to the reduction in the sulfone impurity **5**, the present work also provides a simple and plant-friendly process for the preparation of pantoprazole (**1**). The process is a single-pot reaction in the sense that **1** is isolated in a single shot from the key raw materials. There are no other intermediates isolated in the process. Classical industrial processes involved the isolation of **4** in the form of a solid. It is a low-melting compound, and a large amount of time is consumed in the plant for its drying to proceed to the next step. The present process avoids this problem by dissolving the obtained sulfide (**4**) in an organic solvent followed by its subsequent oxidation using peracetic acid in the same vessel after removal of the aqueous layer without its isolation. The brief outline of the process is described below.

The present reaction involves the condensation of the key raw materials **2** and **3** in water in the presence of sodium hydroxide, wherein compound **4** is precipitated out in the reaction mass as a solid. Further, the obtained sulfide (**4**) is dissolved in an organic solvent and is subjected to oxidation after removal of the aqueous layer in the same vessel using peracetic acid as an oxidizing agent. The peracetic acid (PAA) was added slowly to a solution of **4** in an organic solvent, water, and methanol at temperature of −10 to −5 °C. The intention behind the usage of methanol (0.5 times with respect to dichloromethane) is to enhance the effect of depression of the freezing point of water as the reaction is being carried out at lower temperatures. After the maintenance of the reaction for around 30−45 min, the reaction mixture was quenched in 10% sodium hydroxide solution, and the pH was adjusted between 9.0 and 9.5. Further, the organic layer is separated, which comprises within itself many components including sulfoxide (**1**), unreacted sulfide (**4**), and sulfone impurity **5**, along with some other minor impurities. This organic layer is added to the sodium hydroxide solution and stirred for 10−15 min. Further, the two layers are separated, and the pantoprazole free base is precipitated in the form of a fine solid by adjusting the pH of the aqueous layer between 9.3 and 9.7 in a suitable solvent. Different parameters such as the mole ratio of the peracetic acid, the temperature of the reaction, and the workup conditions were studied thoroughly. The details of the optimization of the various parameters are discussed below in detail.

As per the chemistry involved, an equimolar quantity (with respect to **4**) of the oxidizing agent is required for the conversion of **4** to **1**. The wide range of studies carried out in this direction has thrown light on the fact that the mole ratio of the peracetic acid used plays a vital role in achieving the high purity of the product **1**. The experiments with equimolar quantities of the peracetic acid in the reaction resulted in considerable amounts of **5**. Studies revealed the direct proportionality between the amount of the peracetic acid used and the content of the **5**. A mole ratio of 0.7 equiv of the peracetic acid was found to be the most ideal quantity for the attainment of the required compound **1** with high purity and good yield (Table 2). This table shows the influence of mole ratio of peracetic acid on sulfone (**5**) in a given range of pH (9.3−9.7) and temperature (−10 to −5 °C) at which satisfactory results were obtained during preliminary studies. Even though the yields of **1** were found to be high when 1.0

Table 2. **Effect of mol equiv of peracetic acid**

						purity by HPLC		
exp. no	peracetic acid (mol equiv)	sulfide (mol equiv)	reaction temp (°C)	yield (%)	pH of isolation	**1** (%)	**5** (sulfone impurity) (%)	**4** (%)
1	1.0	1.0	−5 to 0	84.37	9.70	98.29	1.29	0.004
2	0.9	1.0	−10 to −5	78.20	9.46	99.42	0.27	ND
3	0.7	1.0	−10 to −5	76.0	9.48	99.73	0.03	ND
4	0.7	1.0	−10 to −5	76.2	9.54	99.79	0.02	ND

Table 3. **Effect of temperature on the purity of the compound**

expt no	temp (°c)	PAA (mol equiv)	pH of isolation	purity by HPLC		
				1 (%)	**5** (sulfone impurity) (%)	**4** (%)
5	0 to 5	0.7	9.5	98.29	1.09	ND
6	0 to 5	0.7	9.0	98.59	1.10	0.03
7	−5 to 0	0.7	9.5	98.80	0.02	0.05
8	−10 to − 5	0.7	9.32	99.81	0.03	0.01
9	−10 to − 5	0.7	9.62	99.77	0.06	0.01

Table 4. **Effect of pH on the purity % and sulfone content**

expt no.	pH at isolation	PAA (mol equiv)	temp (°C)	yield (%)	purity by HPLC		
					1 (%)	**5** (sulfone impurity) (%)	**4** (%)
10	10.10	0.7	−10 to −5	44.70	99.89	0.06	ND
11	10.09	0.7	−10 to −5	42.19	99.93	0.01	ND
12	9.72	0.7	−10 to −5	68.20	99.78	0.07	0.02
13	9.58	0.7	−10 to −5	61.60	99.77	0.06	0.01
14	9.32	0.7	−10 to −5	68.20	99.81	0.03	0.01
15	9.00	0.7	−10 to −5	69.80	99.34	0.20	ND

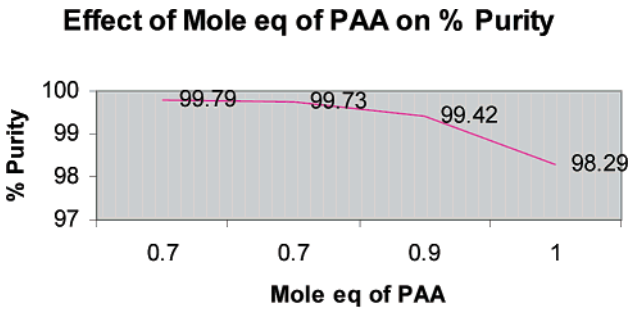

Figure 1. **Graphical representation of experimental results.**

mol of peracetic acid was used, the purity of the compound **1** was not satisfactory. The results of the experiments are depicted in the form of a graph (Figure 1).

After the optimization of the mole equivalents, the next task was the study of the effect of the temperature on the reaction. It was found that the temperature at which the reaction was carried out also proved to be a very important factor in controlling the levels of the impurity **5**. The rate of the formation of impurity **5** is directly proportional to the temperature at which it is carried out. The reaction proceeds very well at even lower temperatures and minimizes the chances of the formation of the sulfone impurity **5** (Table 3). The percent of sulfone impurity **5** was found to be increasing with the increase in temperature. A thorough study made to understand the effect of temperature on the purity of the compound led to the observation that the oxidation carried out at temperatures of −10 to −5 °C produces high-quality compound.

Despite the precautions taken with respect to the mole ratio of the peracetic acid and temperature of the reaction, still there are chances of sulfone impurity **5** remaining in the compound. To ensure the removal of the traces of impurity **5**, unreacted sulfide **4**, and the other unwanted impurities, we have developed a workup process which involves the addition of the reaction mass into a solution of sodium hydroxide, wherein unreacted **4** is extracted neatly into the organic layer. The removal of the unreacted **4** was based on the fact that it has no inclination for the formation of the sodium salt and is left behind in the organic layer, whereas the corresponding sodium salts of compounds **1** and **5** are carried on in the aqueous layer. Further, the aqueous layer containing the salts of **1** and **5** is subjected to pH adjustment in the presence of suitable solvent wherein the compound **1** was selectively isolated in high purity leaving behind the impurity **5** in the aqueous layer due to its solubility at that particular pH, whereas the unreacted **4** is recovered from the organic layer. This process of workup of the reaction was highly efficient in cutting down the unreacted **4**. Studies in the laboratory clearly indicated that compound **4** is removed almost completely from the reaction mixture. In most of the production batches, the compound **4** was not at all detected (see Table 6).

To standardize the optimum pH, a screening study on the pH for isolation of the desired compound **1** was conducted at various pH ranges. At the pH range around 9.3−9.7 the purity of the sulfoxide **1** isolated was good, and the sulfone (**5**) content was found to be negligible. The yields of compound **5** obtained at this pH range were found to be reasonable, but as the pH became more neutral, yields of **1** were high and the percentage of the sulfone impurity **5** was observed to be greater in the precipitated compound (entry no. 15 in Table 4). However, at pH greater than 9.7 there were no adverse affects on the purity of the compound, but the obtained yields were less, as shown in Table 3.

This parameter clearly indicates that, the percent content of impurity **5** in the product **1** and the yields of **1** are inversely proportional to the pH of isolation (as shown in Figure 2, a and b). Meanwhile isolation of the compound by pH adjustment in water alone proved problematic. The nature of the solid obtained was found to be gummy; therefore, simultaneous studies regarding the choice of a suitable solvent for the isolation of the compound in the form of the fine solid crystals were carried out. The results of the

Table 5. **Effect of pH sulfone content during in situ purification**

expt no.	batch size (g)	temp (°C)	pH of isolation	pH of in situ purification	yield (%)	HPLC purity/sulfone content			
						BP[a] (%)		AP[b] (%)	
						1	**5**	**1**	**5**
16	50	−10 to −5	9.54	9.08	80	99.72	0.07	99.77	0.06
17	50	−10 to −5	9.62	9.52	73	99.66	0.13	99.76	0.06
18	50	−10 to −5	9.64	9.72	73	99.66	0.09	99.78	0.04
19	50	−10 to −5	10.18	10.09	55	99.65	0.10	99.93	0.01

[a] BP = Before in situ purification. [b] AP = After in situ purification.

Table 6. **Results of the production batches**

expt. no.	batch input of **3** (Kgs)	temp (°C)	PAA (mol equiv)	yield (%)	pH of isolation	HPLC purity		
						1 (%)	**5** (sulfone impurity) (%)	**4** (%)
20	50	−10 to −5	0.7	79.10	9.3−9.7	99.92	ND	ND
21	50	−10 to −5	0.7	74.20	9.3−9.7	99.92	0.02	ND
22	50	−10 to −5	0.7	74.20	9.3−9.7	99.90	0.01	ND
23	50	−10 to −5	0.7	74.50	9.3−9.7	99.90	0.02	0.007
24	50	−10 to −5	0.7	75.40	9.3−9.7	99.87	0.02	ND

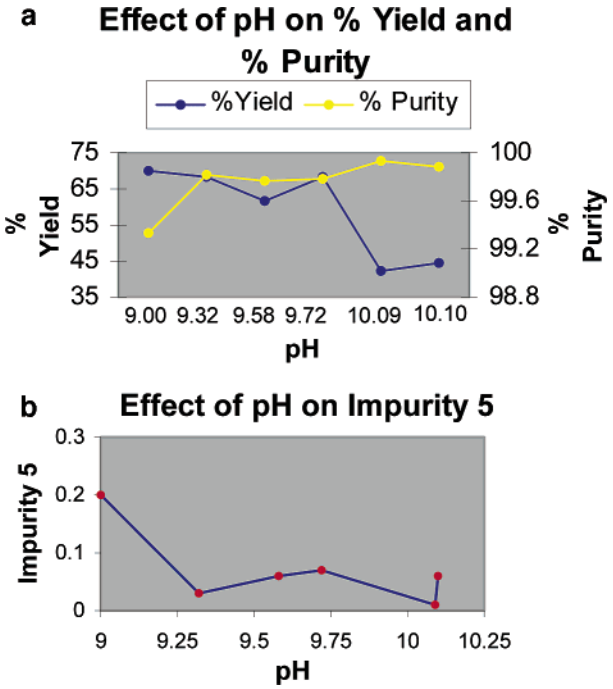

Figure 2. **(a) Graphical presentation of effect of pH on yield and purity. (b) Graphical presentation of effect of pH on impurity 5.**

experiments clearly proved that the solvent that satisfied the need to the best possible extent is acetonitrile. Usage of acetonitrile not only resulted in fine solid crystals but also helped in the minimization of the sulfone impurity. Although the other solvents such as methanol, 2-propanol, butanol, and acetone helped in attaining fine solid, the purity of the compound was found to be best in acetonitrile and water. Thus, acetonitrile was selected in the process.

Further, an in situ purification process comprising the formation of the sodium salt of the compound **1** in acetonitrile and water followed by the pH adjustment between 9.3 and 9.7 resulted in the precipitation of the compound **1** as fine solid crystals. The purity of the resulting compound was found to be extremely good, and the results were consistent. The in situ purification is just a replica of the above conditions, which involves the pH adjustment of the isolated product (wet solid) in the same conditions with respect to the solvent system used (acetonitrile−water). This in situ process has been incorporated as a measure of prevention to remove any remaining traces of impurity **5** in the product. The criticality of the pH range (9.3−9.7) and solvent (acetonitrile) holds well here also as we discussed in the earlier section. However, Table 5 depicts some of the variations of pH during the process of purification, and the results support the observations made.

All the above optimized parameters, viz. mole ratio of the peracetic acid, temperature of the reaction, pH of the isolation, solvent and in situ purification in combination, produced excellent results. The level of the sulfone impurity **5** was found to be always less than 0.05% in all the plant production batches. The results of some of the batches are depicted below in Table 6. The detailed process is described in the Experimental Section.

Conclusions

In conclusion, an efficient and plant-friendly process for the preparation of pantoprazole substantially free from sulfone impurity is described. The fine difference in the nature of compounds **1** and **4** has provided an understanding in the selection of appropriate parameters for the optimization of the process to achieve pantoprazole substantially free from sulfone.

Experimental Section[8]

Synthesis of Compound 1. Into a clean and dry 3-L round-bottom flask was charged sodium hydroxide (44.6 g) followed by water (1 L); the contents were stirred to obtain a clear solution. To the obtained solution was added 5-difluromethoxy-2-mercapto-1H-benzimidazole (2, 99.3 g,

0.46 mol); and the contents were stirred to obtain a clear solution. A solution of 2-chloromethyl-3,4-dimethoxy-pyridinium chloride (**3**, 100 g, 0.47 mol) in water (500 mL) was added dropwise for a period of 1.5−2 h. The contents were stirred for 3−4 h at a temperature of 25−35 °C. Dichloromethane (750 mL) was added, and the contents were stirred to obtain a clear biphasic solution. The aqueous layer was separated and extracted with dichloromethane (300 mL). To the combined organic layer was charged water (600 mL) and methanol (150 mL), and the contents were cooled to −10 to −5 °C. Peracetic acid (148 mL, 0.7 mol equiv with respect to the theoretical yield of **4** obtained in situ) was added over a period of 1−1.5 h, and the contents were stirred for 30−45 min. The reaction mixture was quenched with 10% sodium hydroxide solution (805 mL), and the resulting aqueous and the organic layers were separated. The obtained aqueous layer was extracted with dichloromethane (300 mL), and the organic extract was combined with the main organic layer. Further, the combined organic layer was charged into the sodium hydroxide solution (15 g in 1000 mL of water). The contents were stirred for 30−45 min, aqueous and organic layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 300 mL). Acetonitrile (230 mL) was added to the aqueous layer, and the contents were cooled to 10−15 °C. The pH of the resulting solution was adjusted to 9.3−9.7 using acetic acid. The precipitated solid was maintained for 2−3 h at 0−5 °C, filtered, washed, and sucked dry. The wet solid was recharged into a round-bottomed flask containing a solution of sodium hydroxide (22 g in 600 mL). Acetonitrile was charged (113.0 mL) and the solution stirred for 30−45 min. The pH of the resulting solution was adjusted to 9.3−9.7 using acetic acid at temperatures 10−15 °C. The solid precipitated and was maintained at 0−5 °C for 2−3 h, filtered, washed, and dried. Yield[9] 86%; purity 99.71%; sulfone 0.06%.

(8) Peracetic acid is an effective oxidizing agent having an immense affinity to release nascent oxygen. The product may gradually lose some of its oxidizing power over time. It may get decomposed at elevated temperatures, possibly leading to a hazardous condition. Further, the reagent has mild ill effects on the health of the personnel handling it. It is an irritant and causes strong nasal burns if exposure is not mitigated. Appropriate precautions were taken during its handling in the plant. The substance was stored in a cool and dry location to reduce the chances of exposure to temperature. The reagent was transferred into the reaction mass in a closed system, and general safety measures were taken.

(9) The percent yields of **1** were calculated by considering 70% conversion of the in situ obtained **4** into **1**, as we are using 0.7 mol equiv of peracetic acid with respect to **4** for oxidation.

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