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An Improved Process for the Production of Lansoprazole: Investigation of Key Parameters That Influence the Water Content in Final API†

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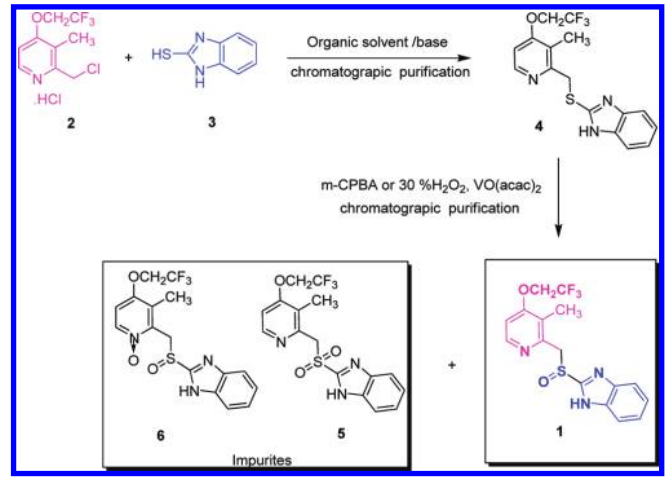
Abstract:

An improved large-scale synthesis of lansoprazole 1 an anti-ulcer drug is described. The synthesis commences with condensation of 2-mercaptobenzimadazole 3 with 2-chloromethyl-3methyl-4-(2, 2, 2-trifluoro ethoxy) pyridine hydrochloride 2 using water as a solvent to yield thioether 4. Subsequently, 4 was selectively oxidized to 1 by using sodium hypochlorite, a mild, economic, and eco-friendly oxidizing agent. A systematic investigation of crystallization parameters in the final stage, which enabled us to control the water content in the final API to <0.10%, were also discussed. (As recommended by USP 28 monograph (*The United States Pharmacopeia: USP 28: NF 23*, 28th rev. of The Pharmacopeia of the U.S., 23rd ed. of The National Formulary; United States Pharmacopeial Convention; Rockville, MD, 2005; p 1110.)

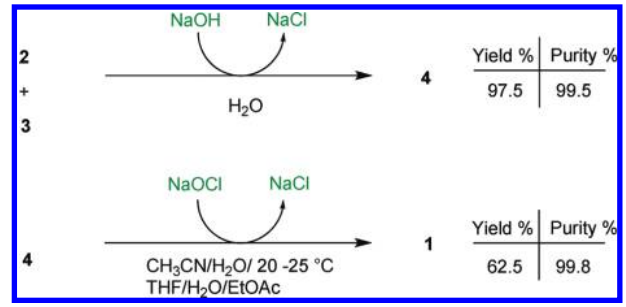
Introduction

Proton pump inhibitors (PPIs) are a group of drugs that elicit pronounced and long-lasting pharmacological effect by reducing the gastric acid production. These drugs are among the most widely marketed drugs in the world due to their outstanding efficacy and safety. Lansoprazole (**1**) is one of benzimidazole derivatives that act as gastric pump inhibitor and therefore used to prevent ulcers.[1,2] The most common approach for synthesis of **1** involves coupling of **3** with **2** in presence of organic solvent and base to afford thioether **4**, oxidation of **4** with *m*-chloroperbenzoic acid (*m*-CPBA) or hydrogen peroxide in chlorinated solvents to furnish lansoprazole **1** (Scheme 1).[2−4] These processes suffer with the following limitations (i) safety and environmental concerns due to usage of either hydrogen peroxide or *m*-CPBA, (ii) demands strict cryogenic conditions (−30 to −20 °C) to control formation of sulfone (**5**) and *N*-oxide (**6**) impurities, (iii) utilizes huge volumes of chlorinated solvents and long processing times that are less attractive for industrial scale, (iv) involves either chromatographic purifications or cumbersome workup/repeated crystallizations to meet the ICH quality of the final active pharmaceutical ingredient (API).[5]

Scheme 1. **Previously reported approaches for lansoprazole**



Scheme 2. **Our improved synthesis of lansoprazole**



In this report we wish to report our efforts in developing an eco-friendly, easily scalable synthesis of **1** by addressing the above drawbacks.

Results and Discussion

The first step of our synthesis commences with condensation of 2-mercaptobenzimidazole **3** with 2-chloromethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine hydrochloride **2** in the presence of sodium hydroxide using water as a solvent to afford thioether compound **4**. The selection of water as a solvent not only provided **4** as a solid in 97.5% yield and 99.5% purity but also served as an eco-friendly media and thus avoided the use of organic solvents, unlike prior reported procedures.[6] On the basis of our previous experience on process development of proton

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pump inhibitors,[7] we were very certain that controlled oxidation of **4** to **1** coupled with a facile workup procedure which safeguards the process impurities is crucial to the success of the synthesis of **1**. Among the available oxidizing agents for oxidation of **4** to **1**, sodium hypochlorite[8] (NaOCl) was found to be an attractive choice in view of (a) mild reactivity, (b) sole byproduct is sodium chloride, (c) low cost, (d) safety in storage. Subsequently, our approach to understand this oxidation step was carried out in the following selected solvents: water, methanol, isopropanol, acetonitrile, ethyl acetate, and acetone using mixtures of aq sodium hypochlorite: aq sodium hydroxide (1.2 equiv each) at 20−25 °C.[9] Among these, acetonitrile and ethyl acetate were found to be good solvents of choice in terms of complete reaction conversion (Table 1).

Table 1. **Solvent screening for thio ether oxidation (4)**

entry	solvent	**1**[a]	**5**[a]	**4**[a]	yield (%)
1	water	0.98	−	97.6	−
2	methanol	14.4	−	38.5	19.2
3	isopropyl alcohol	55.4	−	39.9	76.6
4	acetone	0.5	−	98.5	−
5	ethyl acetate	96.6	1.96	0.74	67.0
6	acetonitrile	97.5	0.03	−	85.0

[a] HPLC purity (%).

The reaction progress in acetone and water was almost negligible. On the other hand reaction progress was found to be very slow and undesirable impurity formation (at RRT 3.0, 3.8, and 4.0 unidentified) was observed in methanol and isopropylalcohol. Finally, opting for acetonitrile as choice of solvent, a systematic screening of the reaction conditions (reaction temperature, reaction time, mole ratio of aq NaOCl/NaOH) was carried out, and the optimum conditions were identified to be 22.5 ± 2.5 °C, 1.5 h, 1.2 equiv (1:1 ratio). Lansoprazole is thermally sensitive, and attempts to isolate the compound through distillation at temperatures >45 °C or hot crystallizations turn the material into pinkish colored product. Thus, an isolation procedure was established which comprises dilution of the reaction mass with water and subsequent pH adjustment to 9.0−9.5 by using 10% acetic acid to afford **1** as a filterable solid in 85% yield and 97.5% purity. An important parameter was observed during establishment of the isolation procedure, wherein a pH of 9.0−9.5 is essential in achieving the good yield and purity of **1** (Figure 1). While the USP 28 monograph[10a] recommends a water content of <0.10% in the final API, our attempt to dry the resultant crude **1** at various

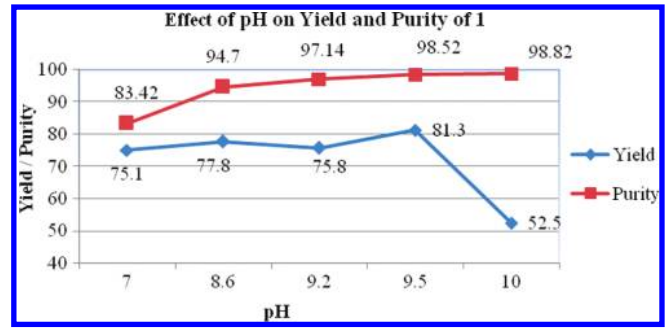

Figure 1. **Graphical representation of experimental results.**

drying conditions (<50 °C) ended always with >2.0% of water content. Thus, we focused on finding a common purification procedure to afford lansoprazole with >99.5% purity and <0.10% of water content.

Purification for Control of Water Content and Impurities in the Final API. In an early screening of the purification procedure, crude product **1** was slurried in selected organic solvents which included ethyl acetate, *n*-hexane, *n*-heptane, cyclohexane, isopropyl alcohol (IPA), acetone, acetonitrile (ACN), and tetrahydrofuran (THF) (Table 2). None of these experiments was found to be fruitful in reducing the water content to <0.10% even after drying with the use of various drying techniques. Although we succeeded in achieving >99.5% purity of **1** by subjecting crude **1** to an ethyl acetate slurry, the required level of <0.10% water content in the sample was not achieved even after prolonged drying (Table 2, entry 4). In the next step, the recrystallization procedure was investigated by using different solvent systems such as acetontrile:H_2O, acetone:H_2O, and THF:H_2O to address the water content. A fine crystalline product with the desired physical properties was obtained when a 1:2 ratio of THF:H_2O was used by dissolving the crude material in 8 volumes of THF followed by dropwise addition of 16 volumes of water as antisolvent.[11] This process yielded **1** with <0.10% of water, whereas the target of >99.5% purity was left undetermined (Table 3, entry 4). Thereafter, the resultant product was suspended in ethyl acetate, and the >99.5% pure solid with <0.10% water content was filtered. In this way, the problems of purity and required water content were addressed.

Thus, the optimized procedure consists of the following: crude lansoprazole **1** was dissolved in THF at 45−50 °C, cooled to 25−30 °C, and water was added about 60−90 min. The suspension was stirred at 5−10 °C for 45−60 min. The solid material was slowly filtered on a pressure nutsche filter (PNF)

Table 2. **Choice of solvent for purification of crude lansoprazole by the slurry method**

	quality of **1** before slurry			drying conditions[c]		quality of **1** after slurry	
entry	purity[a]	water content[b]	solvents screened for slurries	time (h)	temp (°C)	purity[a]	water content[b]
1	97.96	3.0	acetonitrile	12.0	50−55	97.13	0.81
2	95.66	3.0	acetone	8.0	50−55	99.33	0.15
3	98.54	3.0	IPA	8.0	50−55	98.87	1.72
4	93.39	3.0	ethyl acetate	12.0	50−55	99.64	0.30
				24.0	50−55	99.02	0.28
5	98.09	3.7	*n*-hexane	7.0	50−55	98.10	1.14
6	98.31	4.2	*n*-heptane	7.0	50−55	98.35	0.85
7	95.66	1.7	THF	8.0	50−55	97.20	1.72

[a] Area (%) by HPLC. [b] Water content (w/w). [c] Slurried samples were dried in a vacuum tray drier (VTD).

Table 3. **Choice of solvent for purification of crude lansoprazole by recrystallization method**

	quality of **1** before recrystallization			drying conditions[c]		quality of **1** after recrystallization	
entry	purity[a]	water content[b]	solvent:anti solvent	time (h)	temp (°C)	purity[a]	water content[b]
1	97.96	3.0	acetonitrile:H_2O	12.0	50−55	97.13	0.85
2	97.96	3.0	acetone:H_2O	8.0	50−55	97.34	0.14
3	92.50	3.0	MeOH:H_2O	8.0	50−55	94.2	1.72
4	98.30	3.0	THF:H_2O	8.0	50−55	98.8	0.09
				15.0	50−55	98.0	0.08

[a] Area (%) by HPLC. [b] Water content (w/w). [c] All slurried samples were dried in vacuum tray driers (VTD).

Table 4. **Choice of solvent for purification of crude 1 by recrystallization (RC) followed by slurry method**

	quality of **1** before RC		quality of **1** after RC in THF:H_2O			quality of **1** after EtOAc slurries				drying	
entry	purity[a]	H_2O[b]	purity[a]	H_2O[b]	THF[c]	purity[a]	H_2O[b]	THF[c]	filtration equipment	A[d]	B[e]
1	98.30	3.0	98.37	30.0	15,000	99.8	0.03	900	PNF	ND	ND
2	98.30	3.0	98.37	0.10	850.0	99.8	0.10	750	PNF	D	D
3	98.30	3.0	98.37	30.0	15,000	99.8	0.03	320	PNF	ND	D
4	98.30	3.0	98.37	30.0	15,000	99.8	0.5	1300	centrifuge	ND	D

[a] Area (%) by HPLC. [b] Water content (w/w). [c] THF content in ppm (ICH limit: 720 ppm). [d] A: after RC in THF:H_2O. [e] B: after EtOAc slurries; ND: not dried; D: Dried.

Table 5. **Details of scaled up batches in the final purification step of lansoprazole (1)**

			content of residual solvents in **1**[a]				HPLC purity (%)	
entry	crude **1** (kg)	water content (w/w)	MeOH	ACN	EtOAc	THF	**1**	**5**
1	30.0	0.08	37	ND	136	230	99.75	0.10
2	30.0	0.04	62	29	113	452	99.76	0.09
3	30.0	0.06	33	26	124	319	99.80	0.01

[a] Residual solvent limits in ppm: MeOH NMT 3000, acetonitrile (ACN) NMT 410, EtOAc NMT 5000, and THF NMT 720.

and washed with water. The obtained wet solid was suspended in ethyl acetate at 45−50 °C and stirred for 45−60 min. Then the heterogeneous mass was allowed to cool to 5−10 °C for 2−3 h, the slurry was filtered and washed with ethyl acetate, and the wet solid was suspended in ethyl acetate at 45−50 °C and stirred for 45−60 min. Then the heterogeneous mass cooled to 5−10 °C for 2−3 h. The resultant solid was filtered and washed with ethyl acetate and dried to afford lansoprazole **1** in >99.5% purity and <0.10% water content (Table 4, entry 3). Here the choice of filtration equipment was found to be crucial for filtration of the THF:H_2O recrystallized product. Following the above procedure it was noticed that utilization of a centrifuge for filtration of the recrystallized solid gave a hard cake and resulted in higher levels of THF (about 1300 ppm) and water (about 0.5%) in solid **1** and eventually failed to meet the USP/ICH requirements even when employing an ethyl acetate slurry and drying at higher temperature (Table 4, entry 4).[10,12] Presumably, under centrifugation conditions the filtered cake turns hard and leads to trapping of solvent and water in the crystal lattice. In contrast, filtration of the recrystallized product in PNF and subsequent slurring with ethyl acetate always resulted in water content of <0.10%. To our curiosity, a microscopic evaluation of the samples obtained through PNF filtration process and centrifugation process revealed significant differences in morphology (Figure 2).

Finally, from the above studies, the recrystallized (THF:H_2O) product was filtered in PNF and subjected to ethyl acetate slurry which always provides water <0.10% and purity >99.5%. The results of some of the production batches are summarized in

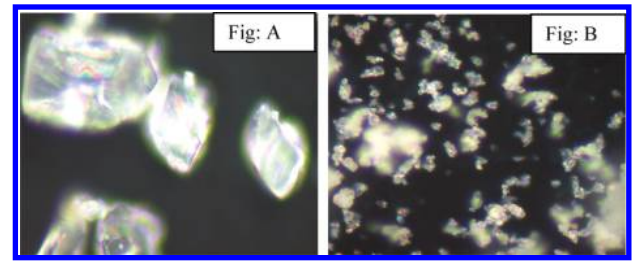

Figure 2. **Microscopic pictures (50× magnification) of recrystallized samples of lansoprazole in (A) THF:H_2O/EtOAc (PNF filtration); (B) THF:H_2O/EtOAc (centrifuge filtration).**

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(9) For all these reactions, commercially available 12.0% aq sodium hypochlorite was used.

Table 6. **Comparative results obtained with the use of a different oxidizing agent[b]**

S. no.	**4** (kg)	oxidizing agent	byproduct	solvent system	reaction time (h)/temp (°C)	yield %
1[a]	40.0	aq NaOCl	NaCl	CH_3CN/H_2O (240 L: 5.4 L)	2/25	62.5
2[b]	40.0	*m*-CPBA	*m*-CBA	$CHCl_3$ (1325 L)	8/−20	57.0

[a] See reference 3a. [b] To evaluate the performance of NaOCl, it was compared with the *m*-CPBA oxidation system.

Table 5. This work has provided a great insight into how the simple filtrations can significantly influence the quality of the API.

Conclusion

In conclusion, we have developed an improved process for production of lansoprazole **1**, anti-ulcer drug, by switching to cheaply available eco-friendly NaOCl in place of expensive *m*-CPBA for oxidation of thio ether **4** (see Table 6 for comparative results). A systematic investigation of crystallization parameters in the final stage enabled us to control the water content in the final API to <0.10% (as recommended by USP 28 monograph[10a]).

Experimental Section

Materials and Instruments. All commercially available materials and solvents were used as received without any further purification. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 at 400 and 50 MHz, respectively, on a Varian Gemini 200 MHz spectrometer. The chemical shift values were reported on δ scale in ppm with respect to TMS (δ 0.00 ppm) and DMSO-d_6 (δ 39.5 ppm) as internal standards, respectively. The ESI mass spectrum was recorded on 4000-Q-trap LC/MS spectrometer. FT-IR spectrum was recorded on Perkin-Elmer model spectrum series FT-IR as KBr pellet. Thermal analysis was carried out on DSC Q1000 of TA Instruments. Microscopic picture study was performed with a Nikon Eclipse 50 *i*pol.

Synthesis of 2-[[{4-(2,2,2-Trifluoroethoxy)-3-methylpyridine-2yl}methyl]thio]-1*H*-benzimidazole Intermediate (4). To a solution of sodium hydroxide (45 kg, 1125 mol, in 300 L water) solution, was added 2-Mercapto benzimidazole **3** (47.2 kg, 314.66 mol), and the mixture stirred at 30−40 °C for homogeneous solution. To this mixture was added 2-chloromethyl-3methyl-4-(2, 2, 2-trifluoroethoxy)pyridine hydrochloride **2** (75.2 kg, 271.7 mol, in 450 L water) solution about 2.0−2.5 h and stirred at 25−30 °C for 2.0−2.5 h. The solid was filtered and washed with water (40 L) to afford wet **4**, subsequently the wet solid **4** was suspended in water (375 L) at 50- 55 °C and stirred for 30−45 min. Then the solid was filtered at 25−30 °C and dried under vacuum to obtain thio ether **4** as off-white solid in 97.5% (94.12 kg) yield with 99.5% HPLC purity.[13] ^{1}H NMR (400 MHz): δ 12.6 (s, 1H), 8.3 (d, J = 5.6, 1H), 7.4 (br, 2H), 7.1 (m, 3H), 4.8 (q, J = 8.8, 2H), 4.7 (s, 2H), 2.2 (s, 3H); Mass: Anal., Calc ($C_{16}H_{14}F_3N_3OS$) (*m*/*z*): 353 and found (M + H) = 354.

Synthesis of 2-[[4-(2,2,2-Trifluoroethoxy)pyrid-2-yl]ethylsulfinyl]-1*H*-benzimidazoles (Crude Lansoprazole). To a suspension of 2-[[{4-(2,2,2-trifluoroethoxy)-3-methylpyridine-2yl}methyl]thio]-1*H*-benzimidazole **4** (40 kg, 113.31 mol) in acetonitrile (240 L) was added sodium hypochlorite (94 kg, 132 mol)/sodium hydroxide/water (5.44 kg, 136 mol/16.8 L) mixture at 20−25 °C about 60−120 min. After maintaining the reaction mass at the same temperature, water (80 L) was added, and the pH was adjusted to 9.0−9.5 by using 10% acetic acid solution (90 L) at 0−10 °C. To this suspension was added water (240 L) and was stirred for 2−3 h at 0−10 °C. The solid material was filtered and washed with water (100 L) and dried at 45−50 °C to constant weight to afford crude lansoprazole **1** in 85% yield (35.5 kg) with 97.5% HPLC purity.[13]

Purification of Crude 2-[[4-(2,2,2-Trifluoroethoxy)-pyrid-2-yl]ethylsulfinyl]-1*H*-benzimidazoles (Lansoprazole). Crude lansoprazole **1** (30 kg) was dissolved in THF (270 L) at 45−50 °C and cooled to 25−30 °C; water (540 L) was added in about 60−90 min. The suspension was stirred at 5−10 °C for 45−60 min. The solid material was slowly (about 60−90 min) filtered on PNF and washed with water (150 L). The thus obtained wet solid was suspended in ethyl acetate (90 L) at 45−50 °C and stirred for 45−60 min. Then the heterogeneous mass was allowed to cool to 5−10 °C for 2−3 h. Then the solid compound was filtered and washed with ethyl acetate (30 L), the wet solid was suspended in ethyl acetate (90 L) at 45−50 °C and stirred for 45−60 min, and then the heterogeneous mass was cooled to 5−10 °C for 2−3 h. The thus obtained solid

(10) For reviews, see: (a) *The United States Pharmacopeia: USP 28: NF 23*, 28th rev. of The Pharmacopeia of the U.S., 23rd ed. of The National Formulary; United States Pharmacopeial Convention; Rockville, MD, 2005; Lansoprazole, p 1110. (b) http://www.usp.org. (c) Robinson, D. *Org. Process Res. Dev.* **2007**, *11* (5), 797–801. (d) Butters, M.; Catterick, D.; Craig, A.; Curzons, A.; Dale, D.; Gilmore, A.; Green, S. P.; Marziano, I.; Sherlock, J.-P.; White, W. *Chem. Rev.* **2006**, *106*, 3002–3027. (e) *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q3C (R3): Impurities: Guidelines for Residual Solvents*; International Conference on Harmonisation, **1997**.

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(12) Attempts were made to reduce water/THF levels with the following input sample: water content 0.5% /THF 1300 ppm. Experimental results: (a) Hot water slurry 1.0%/850 ppm. (b) THF slurry: 0.5%/850 ppm. (c) Drying in rotavapor/air tray drier/vacuum tray drier at 50−55 °C for 20−25 h samples displayed ~0.18−0.2%/750−800 ppm, respectively.

(13) Purity of compound **1** has been determined by RSHPLC analysis [Column YMC-PAK ODS-A 100 mm × 4.6 mm, 3 μ or equivalent, 15 μL; flow rate 1.0 mL/min and injection load 15 μL with a UV detector at 285 nm]. Mobile phase - A: water (100%); mobile phase - B: acetonitrile/water/triethylamine, pH 7.0 [160:40:1 (v/v)]. Diluents preparation: acetonitrile/water/triethylamine, pH 10.5 by *o*-phosphoric acid [40:60:1 (v/v)].

Gradient profile:

time (min)	A (%)	B (%)
0.0	60	40
5.0	60	40
30	40	60
40	20	80
50	20	80
52	60	40
60	60	40

was filtered and washed with ethyl acetate (90 L), and dried to obtain lansoprazole **1** in 74.0% yield (22.2 kg, w/w) with 99.8% HPLC[13] purity. Water content was found by the Karl Fisher method:[14] 0.06% (w/w). Residual solvents MeOH 73 ppm, acetonitrile 29 ppm, THF 319 ppm, and EtOAc 124 ppm were analyzed by gas chromatography.[15] ^{1}H NMR (400 MHz): δ 13.3 (br, 1H), 8.30 (d, J = 6.0, 1H), 7.65 (s, 1H), 7.30 (m, 2H), 7.65 (s, 1H), 7.1 (d, J = 5.6, 1H), 4.9 (q, J = 13.6, 2H), 4.8 (q, J = 8.8, 2H), 2.18 (s, 3H); $_{13}$C NMR (100 MHz): δ 161.2, 154.1, 150.9, 148.1, 143.2, 134.8, 122.1, 123.0, 119.8, 112.6, 64.7, 60.0, 10.5; FT-IR (cm^{-1}): 3235 (−N−H Stretching), 2984, 2930 (Aliphatic −C−H Stretching), 1580 (−C═C Stretching), 1457, 1401 (Aliphatic −C−H Bending), 1173 (−C−N Stretching), 1267, 1039 (−C−O (alkyl ether) Stretching), 972, 750 (Aromatic −C−H Bending); DSC (↓): 178.4 °C; Mass: Anal. Calculated (*m*/*z*): 369.37, (C_{16} H_{14} F_3 N_3 O_2 S), found (M + H): 369.37; CHNS analysis: N = 11.31, C = 51.96, S = 9.31, H = 3.80.

(14) Water content of **1** was analyzed by the Karl Fisher method as mentioned in USP 28[10a] (2.0 gm of lansoprazole and pyridine/ethylene glycol, 8:2 ratios).

(15) Residual solvent analysis of **1** was determined by gas chromatography. [Column AT-Wax, 30 mm × 0.53 mm i.d., 1 μm film thickness, injection volume: 1.0 μL, injector temperature 160 °C, and detector temperature 260 °C, injection mode/ratio: split/1.5. Carrier gas flow used 2.5 psi (Helium). Column initially held at 40 °C for 10 min, then rose to 140 °C at a rate of 10 °C for 1 min, held for 10 min, and then raised to 250 °C at a rate of 45 °C/min and held for 16 min. Headspace conditions: oven temperature maintained at 80 °C, vial equilibration kept for 30 min, loop temperature was 100 °C, and transfer line temperature 110 °C, pressurization for 0.5 min].

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