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An Improved process for Selective Oxidation of Pro-chiral sulfide, A Key Intermediate of Dexlansoprazole

Beeravalli Ramalinga Reddy[1]*, Manoj Kumar Dubey[1], Chittireddy Venkata Ramana Reddy[2], and Rakeshwar Bandichhor[1]

[1]Integrated Product Development, Innovation Plaza, Dr. Reddy's Laboratories Ltd., Bachupally, Qutubullapur, R. R. Dist. 500 072 Andhra Pradesh, India
[2]Center for Environment, Institute of Science and Technology, Jawaharlal Nehru Technological University, Kukatpally, Hyderabad 500 072, India.
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**E-mail: ramalingarb@drreddys.com Telephone: +91 40 44346425, Fax: +91 40 44346164*
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Abstract: An efficient and scalable process was devised for the synthesis of Dexlansoprazole 1 by enantio selective oxidation of pro-chiral sulfide with asymmetric oxidation by modified Kagan's approach. The absolute selective oxidation reaction conditions were established with the help of Design Expert tool. The yield was improved to 90% from 40% of that reported process in selective oxidation reaction.

Keywords: Enantioselective oxidation, Proton pump inhibitor, R-(+) enantiomer, Pro-chiral sulfide, Dexlansoprazole.

Introduction

Dexlansoprazole (*R*)-(+)-([3-methyl-4-(2,2,2-trifluoroethoxy) pyridine-2yl]methylsulfinyl)-1*H*-benzo[*d*]imidazole **(1)** is a proton pump inhibitor developed by Takeda pharmaceuticals. Dexlansoprazole is available as *Dexilant* in the market with 30 mg and 60 mg dosage forms for oral administration. First time United States Food and Drug Administration (USFDA) is approved for the treatment of erosive esophagitis and non-erosive gastro-esophageal reflux disease (GERD or GORD)[1]. Dexlansoprazole is a member of prazole family, includes omeprazole, pantoprazole, lansoprazole and rabeprazole. Dexlansoprazole is the (R)-(+) enantiomer of lansoprazole and it is selectively inhibits the partial cell membrane enzyme (H^+, K^+)-ATPase. It stops the final step of acid production[2] and typically referred as the proton pump inhibitor.

Extensive research work has been published by various groups on asymmetric sulfoxidation

with excellent enantioselectivity; in particular, the oxaziridine mediated asymmetric oxidation is the recent advancement in this area[3]. Astra Zeneca is reported first time selective oxidation of prochiral sulfides to chiral sulfoxides by modifying Kagan's asymmetric oxidation[4] along with detailed mechanistic pathway with the help of Stockholm University research group[5] and its application to prazole family. There are myriad of approaches are known for selective oxidation for the preparation of dexlansoprazole. However we optimized existing synthesis process that consists of two steps as shown in scheme-1[6-7].

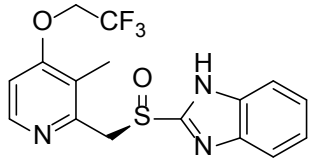

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Figure 1. Structure of Dexlansoprazole

The synthesis commences oxidation of nitrosulphide (**2)** with cumene hydroperoxide in presence of titanium isopropoxide, (+)-diethyl tartrate, diisopropylethyl amine and water followed by purification in acetone and nucleophilic substitution with trifluoroethanol (**4)** in presence of potassium carbonate to afford dexlansoprazole (**1**) with an 29.5% overall yield. The total scheme is given in scheme 1.

In our continuous endeavour of process improvement, we developed an efficient, robust and high yielding process for (**1**) by modifying the original process.

Materials and Methods

All the raw materials, reagents and solvents used in the preparation of dexlansoprazole **1** are commercial grade. IR spectra were carried out by using Perkin Elmer 2400 FTIR spectrophotometer using KBr pellet. Mass spectra recorded on 4000-Q-trap LC-MS/MS mass spectrometer. ^{1}H and ^{13}C NMR were recorded in DMSO-d_6 at 400 MHz on a unity INOVA (Varian 400 MHz) FT NMR spectrometer. The chemical shifts are reported in δ (ppm) relative to TMS (δ 0.00). The SOR was recorded at 25 °C at 1.01 concentration in DMSO.

Results and Discussion

Our objective was to carry out the optimization studies for reagent and solvent quantities used in the complex preparation and optimization of reagents, solvents quantities and reaction conditions during the oxidation of pro-chiral sulfide. In order to understand the existing process three consecutive experiments were conducted using precedented process and found only 70% conversion along with 1% nitro sulphone impurity (**5**). Un-reacted starting material is removed in toluene during the work up and only 60% isolated yield was achieved with 5 - 10% undesired isomer at crude stage. To get undesired isomer less than 2%, compound (**3**) is purified by preferential crystallization using 22 volumes of acetone. During this purification, yield was further reduced to 45 – 55% (**3**) from 60% depends on the undesired isomer present in the compound **3**. Experimental details are tabulated in table 1.

To improve the yield and selectivity during the pro-chiral sulfide oxidation, optimization of sprecedented process using DoE is thought off. Before starting the pre DoE experiments optimization of water and toluene quantity was carried out during the complex preparation and found that 0.3 equivalents of water and 40 volumes of toluene is given best selectivity in sulfide oxidation (table 2).

After finalizing the water and toluene quantities, pre DoE experiments were conducted to find out the factors for DoE. From pre DoE experimental data and FMEA analysis three

Scheme 1. Synthetic scheme of Dexlansoprazole **1**

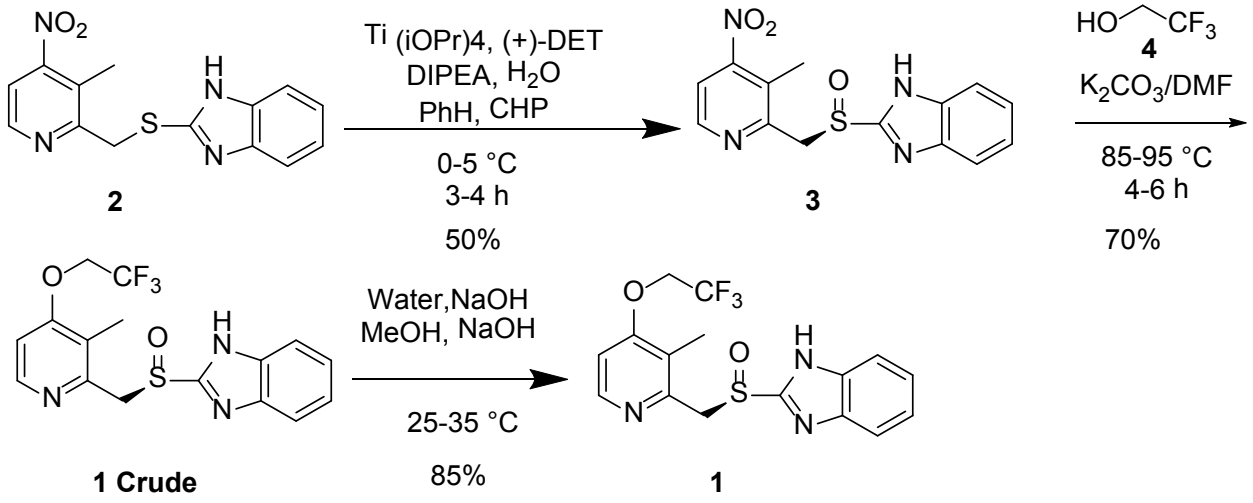


Table 1. Precedented process experimental details

S. No	Batch size (g)	Complex (Eq)	CHP (Eq)	Reaction time (h)	Yield (g)	Yield (%)	Purity (%)	5 (%)	3A (%)
1	50	1.1	1.5	4	30	57	98.7	1.18	8.6
2	50	1.1	1.5	4	29.5	56	99.08	0.67	7.8
3	50	1.1	1.5	4	31.6	60	99.07	0.83	9.1

factors are playing a critical role in achieving higher yield, purity and selectivity, namely equivalents of complex, cumene hydrogen peroxide and reaction maintenance time. Pre DoE experimental details were given in table 3.

Design of Experiments (DoE)

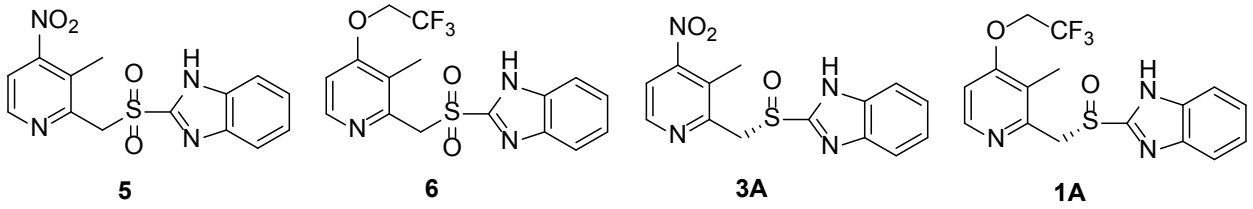


Figure 2. Impurities of Dexlansoprazole

Table 2. Water and toluene quantity optimization during complex preparation

S. No	Batch size (g)	Water quantity in complex (Eq)	CHP (Eq)	Toluene volumes	Yield (g)	Yield (%)	Purity (%)	5 (%)	S-isomer 3A (%)
1	20	0.15	1.5	30	12.6	60	98.77	1.08	3.92
2	20	0.30	1.5	30	18.0	85.5	98.85	0.75	2.82
3	20	0.60	1.5	30	12.0	57.5	98.05	1.36	8.85
4	20	0.30	1.5	40	18.0	85.5	98.20	0.56	1.80

*all reactions maintained for 5 hours -------

Based on pre DoE experimental data, three critical variables are finalized for detailed studies namely mole ratio of complex, cumene hydrogen peroxide (CHP) and reaction maintenance time. Responses selected as yield, purity and chiral purity. Details of variables and responses were given in table 4. Experimental design, model building, analysis and optimization of conditions were performed with the help of Design-Expert software. The design chosen for this case was full factorial with 2^3 + 4 center points experiments along with two replications and total number of experiments=20. All 20 experiments were performed as given by Design expert software and capture the results in figure 3 given by design expert tool.

The obtained results were analyzed by the

Table 3. Pre DoE experimental data

S.No	Batch size	Complex (Eq)	CHP (Eq)	Reaction time* (h)	Yield (g)	Yield (%)	5 (%)	S-isomer 3A (%)
1	20	0.55	1.5	4	17.4	82.8	0.75	1.36
2	20	1.1	1.5	4	15.2	72.4	0.73	2.53
3	20	0.55	1	4	12.2	57.9	0.51	0.86
4	20	0.55	1.5	2	11.6	55	0.29	3.62
5	20	0.55	1.5	8	18	85.5	3.07	1.72

*0 -5 °C temperature for oxidation reaction

Table 4. Variables and Responses for DoE

Process variables			Responses		
Variable-1	Variable-2	Variable-3	Response-1	Response-2	Response-3
Cummene hydroperoxide (Eq's)	Complex (Eq's)	Reaction maintenance time (h)	Yield (%)	Purity (%)	Chiral purity (%)

		Factor 1	Factor 2	Factor 3	Response 1	Response 2	Response 3
Std	Run	A:Chp	B:Complex	C:Rean main time	Yield	Purity	Chiral purity
		moles	Moles	hours	%	%	%
5	1	1.4	0.4	4	78.5	98.9	99.2
18	2	1.5	0.3	5	85.5	98.48	98.5
17	3	1.5	0.3	5	85.8	98.51	98.5
2	4	1.4	0.2	4	78.5	99	97.8
9	5	1.4	0.2	6	82.5	98.75	97.7
19	6	1.5	0.3	5	84	98.6	99.3
8	7	1.6	0.4	4	90	98.15	99.25
15	8	1.6	0.4	6	92	97.85	99.3
7	9	1.6	0.4	4	89	98.05	99.28
10	10	1.4	0.2	6	81.5	98.7	97.7
14	11	1.4	0.4	6	83	98.55	99.25
12	12	1.6	0.2	6	91.5	97.6	97.8
1	13	1.4	0.2	4	77.5	99.05	97.8
6	14	1.4	0.4	4	78.8	98.95	99.3
4	15	1.6	0.2	4	90	98.25	97.75
3	16	1.6	0.2	4	89.5	98.2	97.8
20	17	1.5	0.3	5	85	98.53	98.6
16	18	1.6	0.4	6	92.5	97.9	99.3
13	19	1.4	0.4	6	82.5	98.6	99.28
11	20	1.6	0.2	6	92	97.95	98.15

Figure 3. DoE experimental data

analysis of variance method and a significant model was derived. Similarly the curvature and lack-of fit are non-significant. The effect of the variable in the responses analyzed by ANOVA are shown in the following figures.

After analyzing the full factorial experiments,

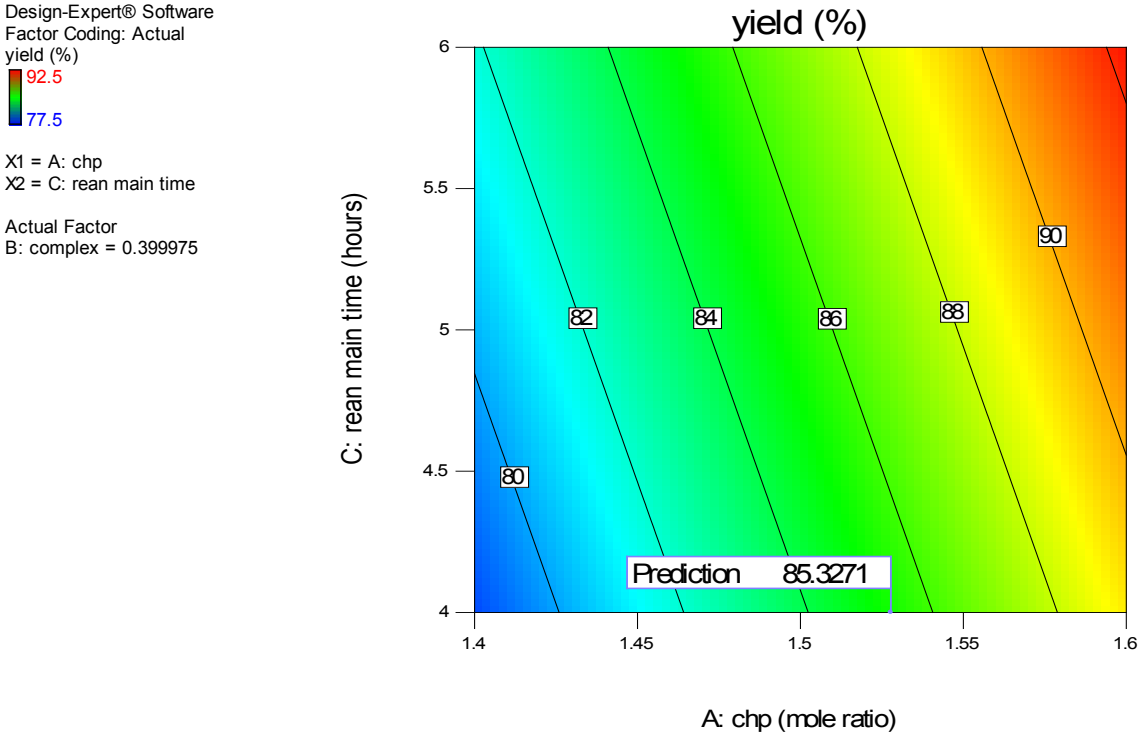


Figure 4. Contour plot for the desirability of yield

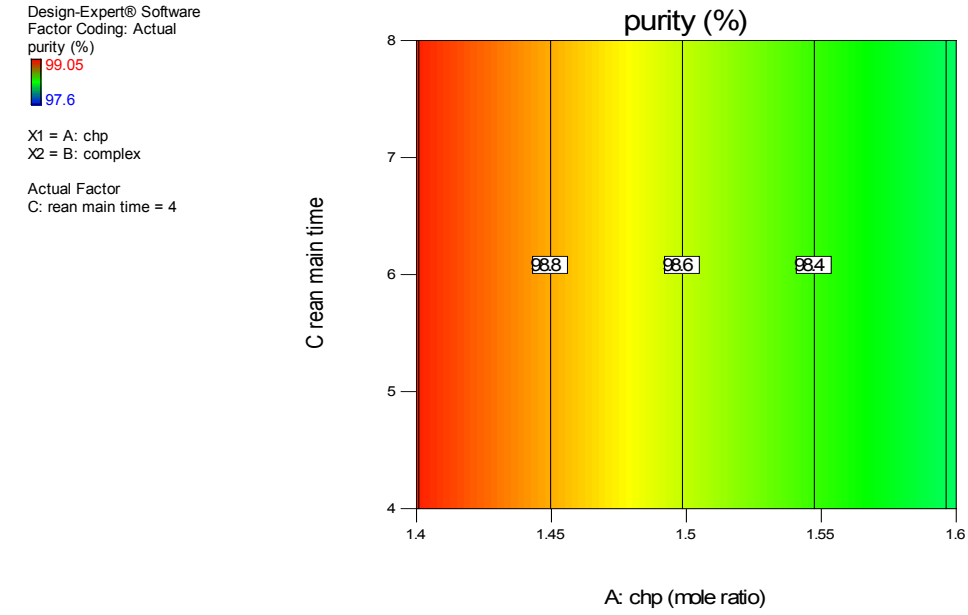


Figure 5. Contour plot for the desirability of purity

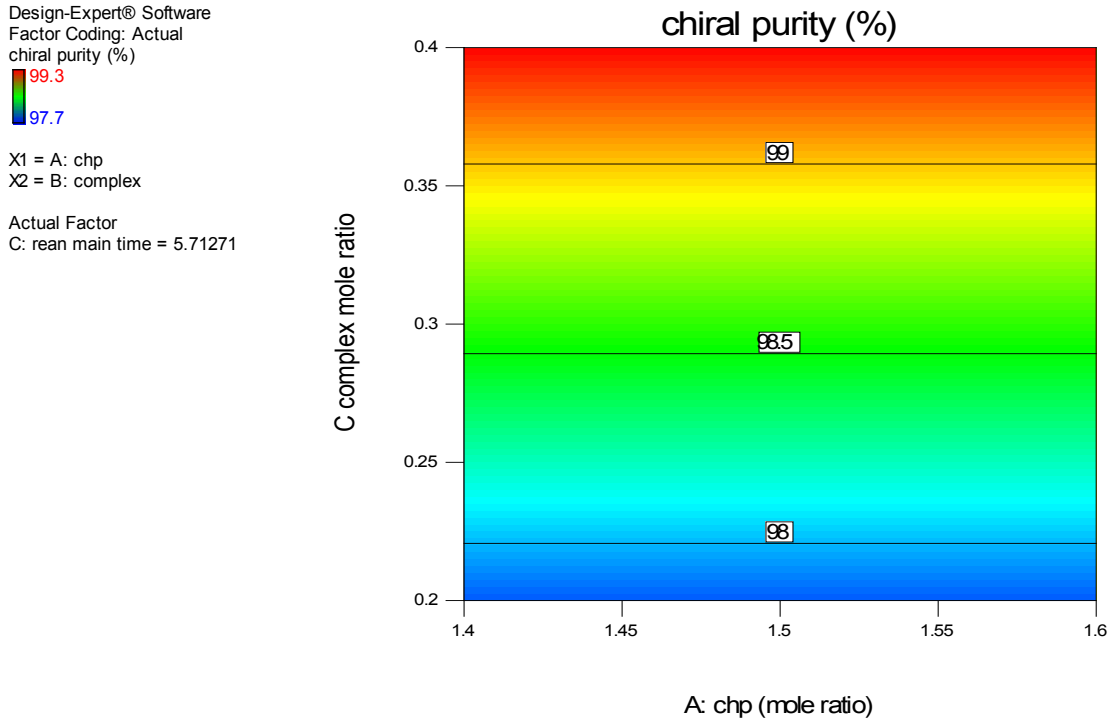


Figure 6. Contour plot for the desirability of chiral purity

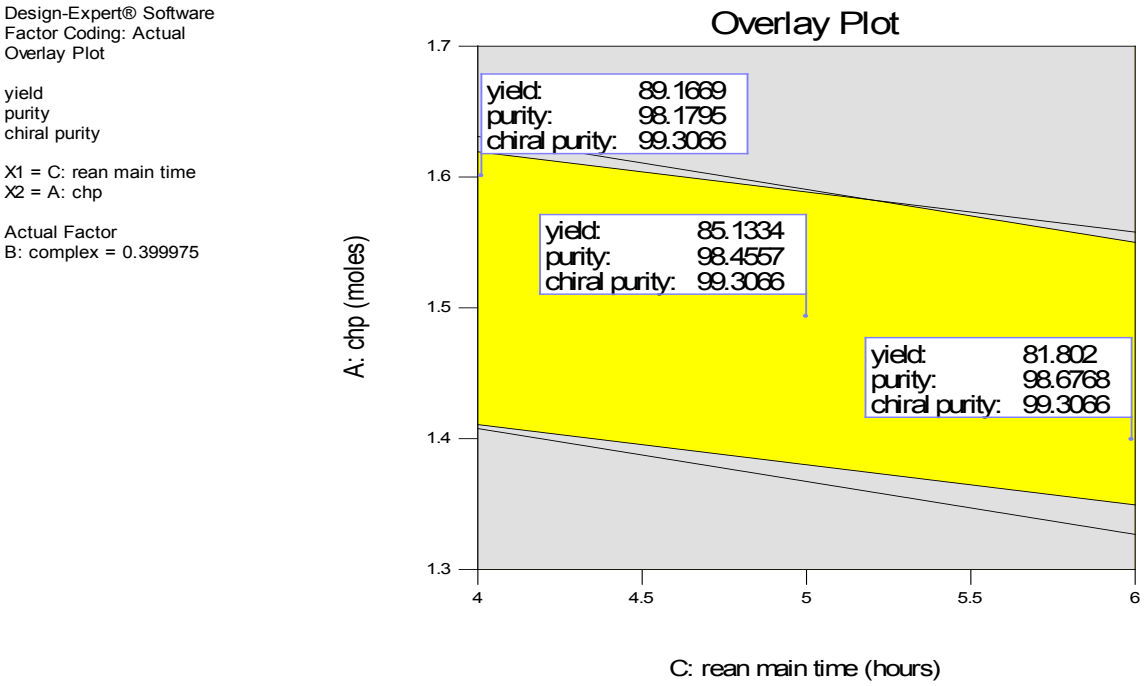


Figure 7. Overlay plot of design space given by DoE

Table 5. DoE validation experiments

S.No	Input (g)	Complex (Eq)	CHP (Eq)	Main. (h)	Predicted responses for compound 3			Obtained responses for compound 3		
					Yield (%)	Purity (%)	Chiral purity (%)	Yield (%)	Purity (%)	Chiral purity (%)
1	50	0.30	1.4	6.0	89.2	98.18	99.30	90.3	98.25	99.27
2	50	0.30	1.5	5.0	85.2	98.45	99.30	86.0	98.69	99.29
3	50	0.30	1.6	4.0	81.8	98.67	99.30	82.5	98.85	99.39

only CHP mole equivalents and reaction maintenance time are playing a key role in achieving the yield and purity while complex mole equivalents is playing important role in achieving desired selectivity. More than 80% yield, 97% purity and 98% chiral purity are considered for design space.

DoE validation experiments were conducted based on design space given by software. The design space given by the software was shown in figure 7. Experimental details of predicted Vs actual are given in table 5.

Excellent correlation was observed between predicted and actual experiments, in addition to this suitable operating limits for the three variables were achieved using individual design spaces for the reaction as represented in the figure 7.

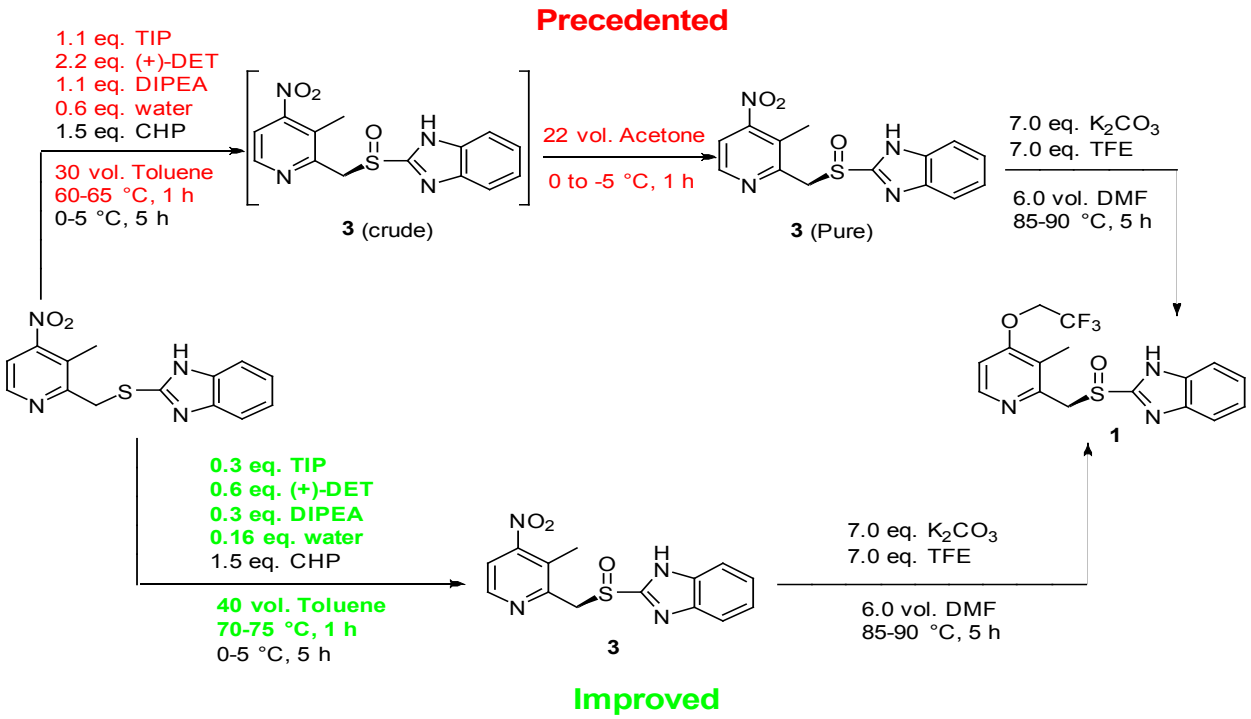
After achieving a robust process for oxidation, we shifted our focus to eliminate preferential crystallization step. In precedented process[7], the chiral purity of the compound (**3)** is in-between 90-95%. To get the chiral purity more than 98%, recrystallization of intermediate **3** from acetone is required. Where as in proposed process chiral purity is more than 98% during the oxidation itself and additional purification in acetone is eliminated from the process.

Proposed process nitro sulfoxide (**3**) is converted to dexlansoprazole (**1**) in existing reported process and experimental results are tabulated in Table 6. The green matrix calculations and graphical representations for compound **3** are shown in table 7 and figure 8.

After completing the lab development proposed

Table 6. Yield and quality of **1** using **3** prepared in proposed process.

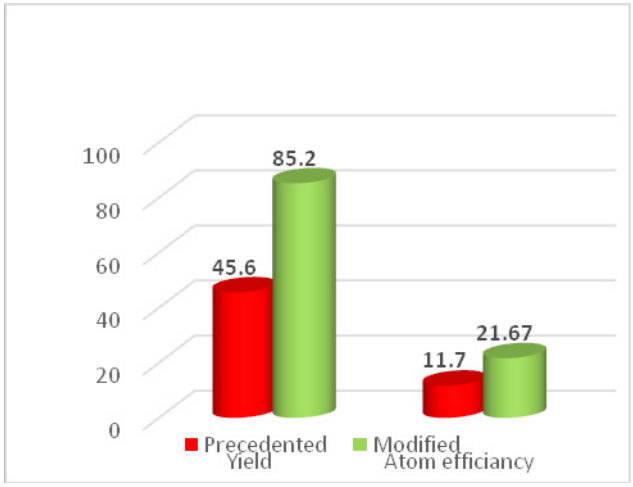
S. No	Batch size (g)	Yield (g)	Yield (%)	Purity (%)	Sulphone (6) (%)	*S*-isomer (1A) (%)
1	30	25.0	71.4	99.69	0.15	0.02
2	30	24.6	70.3	99.71	0.15	0.02
3	30	24.6	70.3	99.75	0.11	0.02

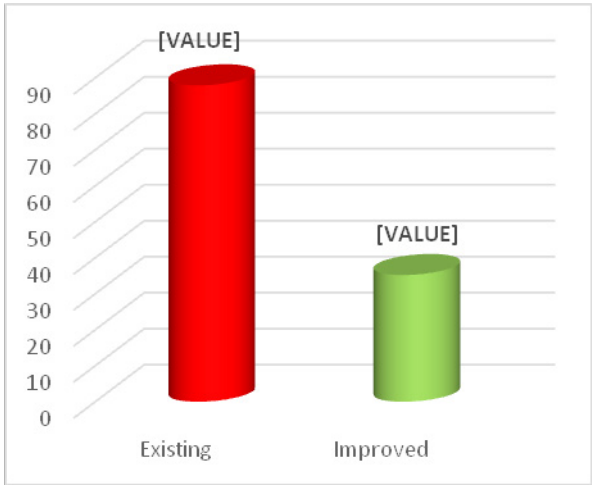


Scheme 2. Comparison of precedented and improved process synthetic scheme

Table 7. Green matrix calculations

	Yield (%)	Atom efficiency (0 – 100 scale)	E-Factor Kg)
Precedented	45.6	11.7	87.9
Improved	85.2	21.7	35.2





Yield & atom efficiency **E-Factor**

Figure 8. Green matrix graphical representations for compound **3**

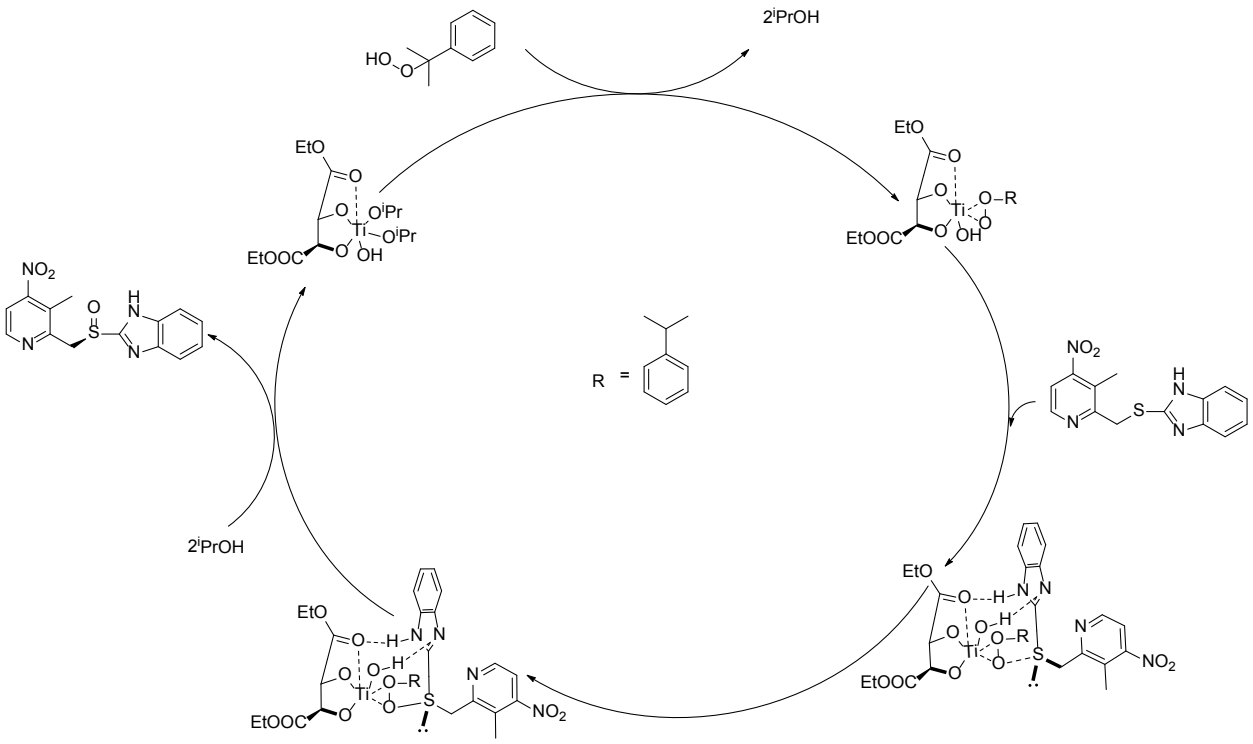


Figure 9: Plausible mechanism of selective oxidation

Table 8. Yield data of the commercial batches

S. No	Batch size (Kg)	Complex (Eq)	CHP (Eq)	Rxn. Main. (h)	Compound 3		Compound 1	
					Yield (Kg)	Yield (%)	Yield (Kg)	Yield (%)
1	25	0.3	1.5	5	22.6	86.1	18	71
2	25	0.3	1.5	5	22.4	85.3	17.6	70
3	25	0.3	1.5	5	22.3	85	18.3	73

Table 9. Quality data of commercial batches

S. No	Compound 3 quality data			Compound 1 quality data		
	Purity (%)	Sulfone (4) (%)	Chiral purity (%)	Purity (%)	Sulfone (5) (%)	Chiral purity (%)
1	97.13	0.55	98.62	99.69	0.15	100
2	97.96	0.51	98.99	99.71	0.11	100
3	97.79	0.86	98.29	99.75	0.15	100

process is tested at plant scale also using 0.3 equivalents of complex, 1.5 equivalents of CHP with 5 hours reaction maintenance time during oxidation to achieve the higher yield with in the design space. Commercial batches details are given in table 8 and 9. Based on the available literature on the complex structure and the improved reaction conditions, a plausible structure of the complex was proposed in a catalytic cycle. The catalytic cycle was shown

in figure 9.

Conclusions

In conclusion an efficient, robust, high yielding process is developed for the preparation of Dexlansoprazole (**1**) by establishing the optimum reaction conditions for selective oxidation of the pro-chiral sulfide to sulfoxide. This process is tested at plant scale also and results are similar to laboratory. The optimized oxidation protocol is also suitable for the selective oxidation of other sulfides like Omeprazole, Pantoprazole and Rabeprazole with minor modifications.

Experimental section

All reagents were obtained from commercial sources used in the plant as well as in the RCI. A liquid chromatograph equipped with variable-wavelength UV detector and integrator was used in recording HPLC spectra. Commercial solvents and the reagents were used without further purification. Titanium tetraisopropoxide is clear solution which is free from Titanium oxide.

Preparation of R-(+)-2-(4-Nitro-3-methyl-pyridin-2-ylmethanesulfinyl)-1*H*-benzimidazole (Compound 3).

Compound **2** (105.5 g 0.35 mole) was taken along with Toluene (4.2 L) in a RBF arranged in azeotrope reflux mode. The solution was heated to azeotrope reflux (109 - 111 °C) and maintained at the same temperature for 60 min. Then cooled the mass to 70 - 75 °C, charged with titanium isopropoxide (28.17 g 0.10 moles), (+)-diethyl tartrate (41.2 g 0.20 moles) and water (0.97 mL, 0.053 moles). Stirred the contents at the same temperature for 60 min. Again cooled the mass to 15 °C and charged with DIPEA (12.7 g 0.10 moles) followed by cooling to 0 - 5 °C. Then cummene hydroperoxide (86.4 g, 0.50 moles assay 88%) was added at 0 - 5 °C for 20 min followed by maintained the reaction at 2 - 3 °C for 4 - 5 h. The progress of the reaction (>95%) was monitored by TLC. A 12.5% aqueous Piperidine solution (1.0 L) was added to reaction mass at below 10 °C. The temperature was raised to 25 - 30 °C and separated the phases. The organic phase was re-extracted with 12.5% piperidine solution (1.0 L) followed by 12.5% aqueous Ammonia solution (2x1.0 L). The product gets extracted in the aqueous phase. The aqueous phases were mixed and washed with Toluene (2x250 mL) to remove the unreacted sulfide. Acetonitrile (600 mL) was charged to the aqueous phase followed by cooling to 10 - 15 °C. The pH of the mass was adjusted to 8.5 - 9.0 with acetic acid at 10 - 15 °C. The contents were stirred at the same temperature for 30 min. The temperature of the mass was raised to 25 - 30 °C and stirred for 2 h. The precipitated product separated by filtration, washed with water (500 mL). The obtained material was dried in air tray drier at 45 - 50 °C for 5 h affords 94.7 g (85.2% yield) with 98.8% purity by HPLC and 99.3% chiral purity by chiral HPLC. Mass: 317 $(MH)^+$; IR (KBr, cm^{-1}): 3425, 3067, 3049, 2977, 2949, 2810, 1678, 1560, 1545, 1459, 1439, 1370, 1165, 803, 782, 744, 735; ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 2.44 (s, 3H), 4.96 (dd, 2H), 7.32 (m, 2H), 7.65 (m, 2H), 7.8 (d, 2H), 8.6 (d, 1H), 13.5 (bs, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz, δ): 14.1, 39.3, 39.5, 39.7, 39.9, 40.1, 40.3, 40.5, 60.1, 116.6, 123.8, 125.9, 148.8, 154.1, 154.4, and 156.8.

Preparation of R-(+)-2-([3-methyl-4-(2,2,2-trifluoroethoxy)pyridine-2-yl] methylsulfinyl) -1*H*-benzo[*d*]imidazole (Compound 1).

Charged compound **3** (90 g 0.285 moles) along with dimethyl formamide (900 mL), Potassium carbonate (275.4 g 2.0 moles) and trifluoroethanol (199 g 2.0 moles) in a RBF arranged in reflux mode. Heated the mass to 85 - 90 °C and maintained the reaction contents

at the same temperature for 4 h. The progress of the reaction was monitored by HPLC. The reaction mass was cooled to 30 °C, filtered to remove the inorganics. The inorganic salt was washed with acetonitrile (360 mL). The filtrate was charcolized with activated charcoal (27.0 g) at 65 - 70 °C. The mass was filtered through celite bed and washed with water (900 mL). The obtained filtrate was taken in a fresh RBF and cooled to 5 - 10 °C. The reaction mass pH was adjusted to 8.3 - 8.7 with dilute acetic acid solution. The reaction mass was aged at the same temperature for 2 h. The isolated solid was separated by filtration and washed with water (500 mL). The obtained wet intermediate was stirred at ambient temperature in water (540 mL) for 1 hour. The product was separated by filtration and washed with water (180 mL). The obtained product was dried at 45 - 50 °C for 10 h under reduced pressure to obtain 79 g (75.18% yield) with 99.65% purity by HPLC & 99.89% chiral purity by chiral HPLC as off-white crystalline solid. Mass: 370 $(MH)^+$; IR (KBr, cm^{-1}): 3400, 3072, 2976, 2898, 1584, 1474, 1443, 1165, 1051, 973, 743; ^{1}HNMR (DMSO-d_6, 400 MHz, δ): 2.17 (s, 3H), 4.75 (dd, 2H), 4.87 (m, 2H), 7.08 (d, 1H), 7.30 (m, 2H), 7.6 (bs,2H), 8.28 (d, 1H), 13.56 (bs, 1H). ^{13}CNMR (DMSO-d_6, 100 MHz, δ): 11.0, 39.3, 39.5, 39.7, 39.9, 40.1, 40.3, 40.6, 60.4, 64.6, 64.9, 65.3, 65.6, 107.5, 122.5, 122.8, 123.7, 125.6, 148.6, 151.4, 154.6 and 161.8.

Supporting Information Summary

General information, spectral data and green matrix calculations.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

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