Organic Process Research & Development

Communication

pubs.acs.org/OPRD

Improved and Efficient Process for the Production of Highly Pure Iloperidone: A Psychotropic Agent†

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ABSTRACT: The present work describes an improved and highly efficient process for the synthesis of iloperidone (**1**), an antipsychotic agent, which is free from potential impurities. The synthesis comprises *N*-alkylation of 1-(4-(3-chloropropoxy)-3-methoxyphenyl)ethanone (**4**) with 6-fluoro-3-piperidin-4-yl-1,2-benzisoxazole hydrochloride (**5**) in a mixture of water and heptane as solvent and sodium hydroxide as a base in the presence of tetrabutylammonium bromide as a phase transfer catalyst to yield iloperidone (**1**) with a yield of around 95% and a purity of 99.80% by HPLC. The present work also describes the optimization details performed to achieve the process attributes responsible for high yield and purity.

INTRODUCTION

The use of generic drugs is steadily increasing globally as a result of economic pressure on drug budgets, as they provide the opportunity for major savings in healthcare expenditures, since they are substantially lower in price than the innovator brands.[1] Hence, Process Research and Development in pharmaceutical companies aims to develop processes for the manufacture of chemical intermediates or active pharmaceutical ingredients (APIs) at minimal cost with high yield and quality. There are many challenges that may limit the competitiveness and sustainability of the generic API manufacturer. The challenges in generic API development are increasing day by day due to better patent protection by originators for compounds, processes, impurities, intermediates, salts, polymorphs, particle size distributions (PSDs), formulations, and new indications. Thus, the development of processes for chemical intermediates and APIs is no longer an easy task for the chemist due to increasing technical difficulties, synthetic challenges, sustainability of the processes in terms of greener chemistry, cost barriers throughout the life cycle of the product, genotoxic control, polymorph control, and regularly growing regulatory hurdles such as ICH Q11, QbD, longer registration steps, and tightened quality control. Hence launching of product with all the above considerations at a low cost of the API is a key to success the first time rather than switching later on. Identification and control of impurities is a never ending task in the life cycle of the product due to continuous changes in raw materials, vendors, change in processes under cost improvement programs, etc. The various sources of impurities in pharmaceutical products are reagents, heavy metals, ligands, catalysts, other materials, such as filter aids, charcoal, and the like, degraded end products obtained during\after manufacturing of bulk drugs from hydrolysis, photolytic cleavage, oxidative degradation, decarboxylation, enantiomeric impurities, and so on. It is important to give greater consideration to these detrimental impurities. Thus, the investigation of impurities in APIs presents a significant analytical challenge for the detection, quantization, and characterization of the compounds alone. Many times, formation of the impurities can be controlled or reduced during the reaction by understanding the kinetics of the reaction and root cause for the formation of impurities so that formation of impurities can be suppressed rather than addressing it at a later stage by multiple purifications. We report an improved and efficient process for production of highly pure iloperidone (**1**), addressing the above issues.

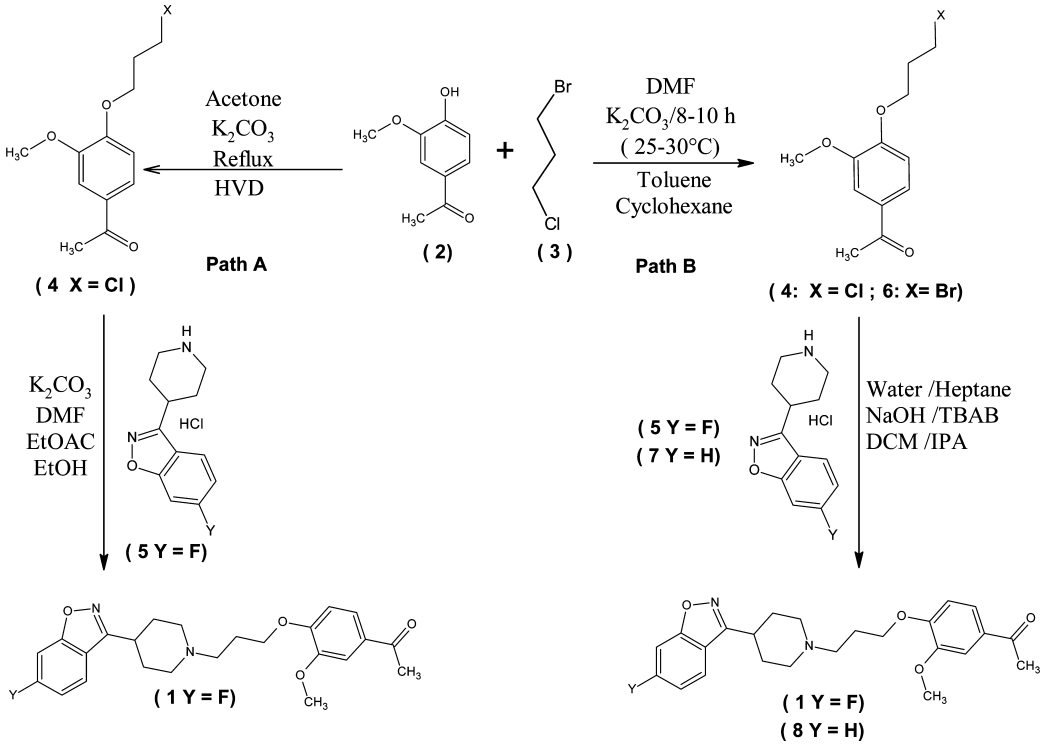
Iloperidone (**1**), chemically designated as 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone, is a second generation atypical antipsychotic agent. Iloperidone, also known as Fanapt, Fanapta, and Zomaril, was approved by the U.S. Food and Drug Administration (FDA) for use in the United States on May 6, 2009 and is indicated for the acute treatment of schizophrenia in adults. Iloperidone has been shown to act as an antagonist at all tested receptors. It was found to block the sites of noradrenalin (α2C), dopamine (D2A and D3), and serotonin (5-HT1A and 5-HT6) receptors.[2] In addition, pharmacogenomic studies identified single nucleotide polymorphisms associated with an enhanced response to iloperidone during acute treatment of schizophrenia. It is considered an "atypical" antipsychotic because it displays serotonin receptor antagonism, similar to other atypical antipsychotics. The older typical antipsychotics are primarily dopamine antagonists.[3]

The synthetic method reported[4,5] for **1** involves two chemical steps: *O*-alkylation of acetovanillone (**2**) with 1-bromo-3-chloropropane (**3**) to obtain chloro derivative **4** followed by *N*-alkylation of piperidine intermediate **5** with **4**. The reported process for **4** comprises *O*-alkylation of **2** with **3** in acetone in the presence of potassium carbonate for 20 h to provide **4** as an oil after usual work up, which was then vacuum (0.1 mmHg) distilled to collect desired product **4** at 141−143 °C with around 85% yield (Scheme 1, Path A). Some of the drawbacks of this process are as follows: longer reaction time (around 20 h), formation of 6−7% of dimer impurity (**10**, Scheme 2), high-vacuum distillation to achieve the quality, which is always a cumbersome process at industrial scale, requiring special apparatus and skill set, and degradation and charring of some portion of product during high-vacuum distillation. Further, the next step comprises *N*-alkylation of **4**

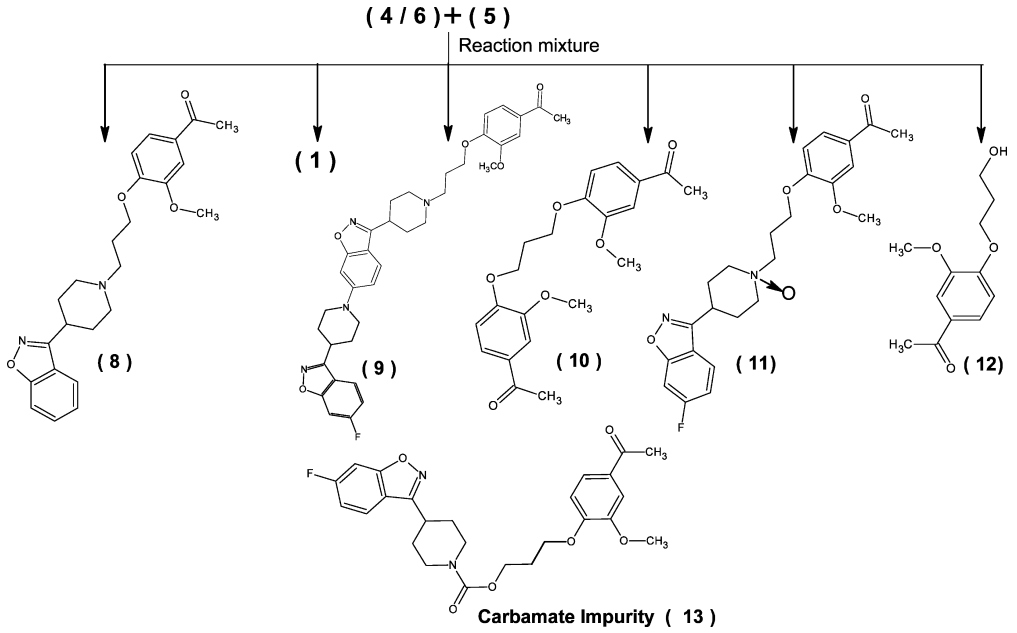
Received: November 27, 2013
Published: January 6, 2014

dx.doi.org/10.1021/op400335p | *Org. Process Res. Dev.* 2014, 18, 342−348

Scheme 1. Reported (Path A) and Improved (Path B) Process for Preparation of 1



Scheme 2. Flow Chart Representing the Formation of Impurities



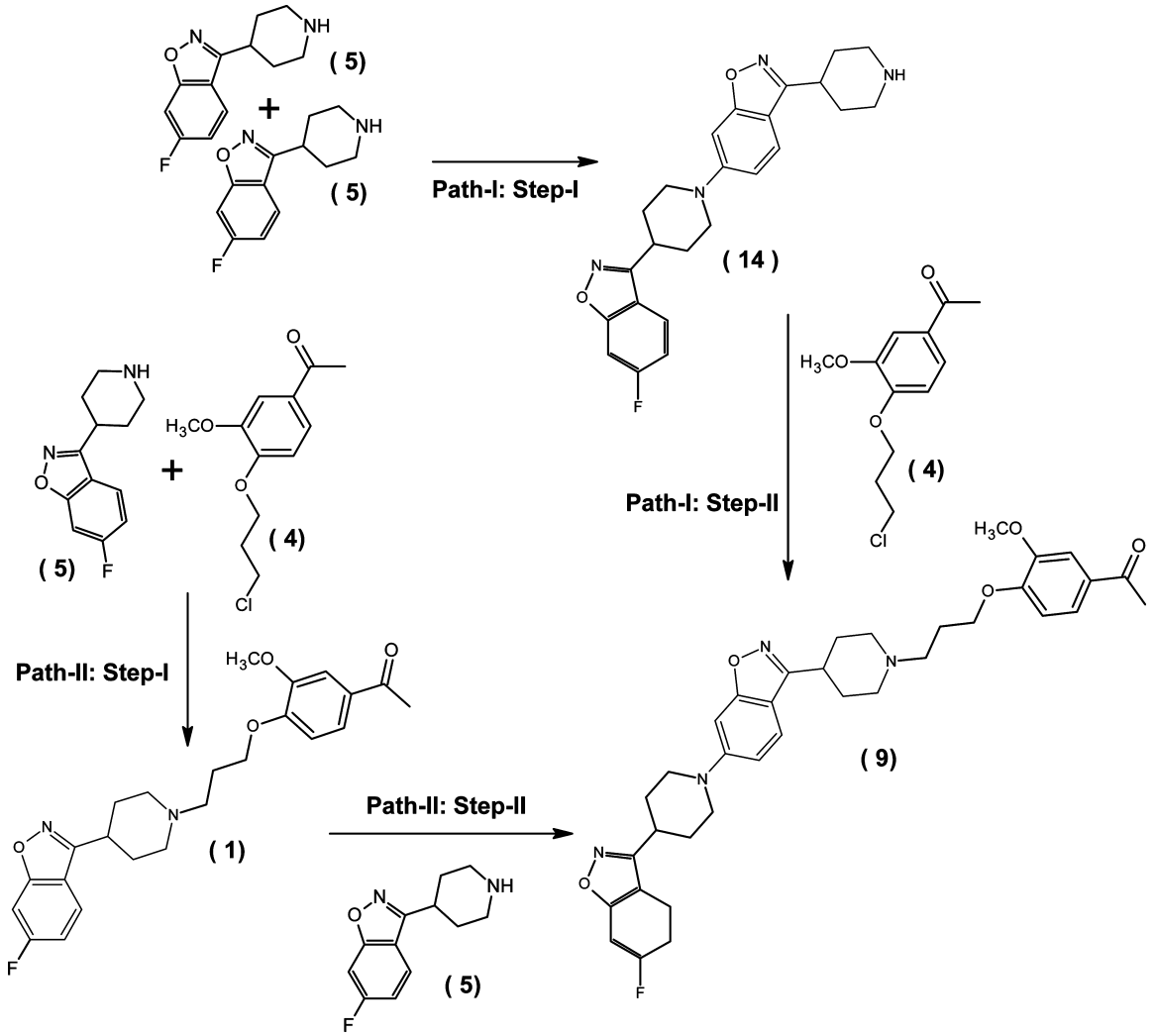
(Impurity 13 was formed as per the literature reported process for manufacturing of iloperidone)

with **5** in *N*,*N*-dimethylformamide (DMF) in the presence of potassium carbonate to provide iloperidone (**1**) as a crude solid, which was purified by crystallization using ethanol to yield pure **1** with 58% yield (Scheme 1, Path A). Some of the lacunae observed with the above process includes the following: (a) low yields, (b) formation of carbamate impurity **13** (Scheme 2) in the range 15−20% due to the use of potassium carbonate, (c) ineffective purification by crystallization using ethanol to eliminate carbamate impurity below 0.15%, and (d) iloperidone obtained by the above synthetic process was beige in color.

A few other improved processes reported subsequently for **1** follow the same reaction sequence (Scheme 1, Path A) using compounds **4** and **5** as key starting materials with different bases and solvents.[6−13] However, the reported processes do not address a control mechanism for impurities **8**, **9**, **11**, and **13** (Scheme 2) formed during the synthesis of **1**. In order to eliminate these impurities, the reported processes involve employment of multiple purifications using a single solvent or

dx.doi.org/10.1021/op400335p | *Org. Process Res. Dev.* 2014, 18, 342−348

Scheme 3. Synthetic Route for the Formation of 9



mixture of solvents or purification by means of formation of the acid addition salt of **1** followed by converting back to pure **1**.[6−13] All the reported processes are low yielding, which reduces the throughput, efficiency, and sustainability of the process throughout the life cycle of the product. Hence, we felt the need for an improved, cost efficient, and impurity free process for the commercial production of **1**.

In order to overcome the above-mentioned limitations, we thoroughly understood the root cause for the formation of each individual impurity and then optimized the process with different solvents, different bases, mole ratio, reaction time, and temperature. Among the various solvents tested for *N*-alkylation of **5** with **4**, the mixture of water and heptane as a solvent provided encouraging results with respect to yield and quality. Remarkable improvement in the quality is achieved when sodium hydroxide is used as base in the presence of a phase transfer catalyst, tetrabutylammonium bromide (Scheme 1, Path B).[14] This combination of solvent and base completely eliminated the formation of carbamate impurity **13** and *N*-oxide impurity **11** and controlled the formation of dimer impurity **9** to an acceptable limit as per ICH guidelines. Another advantage of our process lies in its environmental friendliness, with removal of impurities in a single step with a minimum amount of solvent (5−6 volumes per gram of crude **1**).

RESULTS AND DISCUSSION

Preparation of 4. Intermediate **4** was prepared according to a literature process[4] with process modifications and improvements (Scheme 1, Path B). The *O*-alkylation reaction of **2** with **3** was performed in DMF in the presence of potassium carbonate at ambient temperature (25−30°) for 8−10 h. The reaction mixture was quenched over water, and the product was extracted in toluene. The toluene layer was washed and distilled under vacuum to yield the crude **4**, which was then crystallized using a mixture of toluene and cyclohexane to provide pure **4** as a low-melting solid. The dimer impurity **10** was controlled below 0.5% in **4** without high-vacuum distillation.

Preparation of 1. The benzisoxazole intermediate **5** was prepared as per the literature procedure.[15] Condensation of **4** and **5** is a key and critical step in the synthesis of iloperidone (**1**); hence, we explored the reaction with different solvents (i.e., DMSO, DMF, acetone, acetonitrile, methanol, water, and toluene) using organic bases (i.e., pyridine, triethylamine, dimethyl amine, diethyl amine, diisopropylamine, diisopropyl ethyl amine) and inorganic bases (i.e., sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, cesium carbonate, sodium hydroxide, and potassium hydroxide) to establish the effect of solvents and bases on

dx.doi.org/10.1021/op400335p | Org. Process Res. Dev. 2014, 18, 342−348

the alkylation reaction. The reactions were found to be slow when organic bases are used in various solvents and did not go to completion even after 55 h at ambient as well as reflux temperature. The carbamate impurity **13** was suppressed when organic base was used, but formation of dimer impurity **9** was still an issue. Reaction in acetonitrile using potassium carbonate as a base furnished crude **1** with about 85% yield having about 0.14% of dimer impurity **9** and 0.34% of carbamate impurity **13**, which are critical to remove. Further, we conducted few reactions using alkalimetal hydroxides and alkalimetal carbonates as a base and water as a solvent wherein we observed that with the combination of alkalimetal carbonate especially potassium carbonate as a base and water as a solvent lead to the formation carbamate impurity **13** up to 1.5%. Surprisingly, when the reaction was performed using sodium hydroxide or potassium hydroxide as a base and water as a solvent, *N*-oxide impurity **11** and carbamate impurity **13** were totally suppressed and critical dimer impurity **9** was observed up to a level of around 0.13−0.15% with a yield of around 93% and purity of around 96%. Further, it was observed that reaction was very slow in water in the presence of sodium hydroxide as a base at the temperature 55−60 °C and took around 20−25 h for completion, with the formation of dimer impurity **9** around 0.15%. The raise in reaction temperature to 65−70 °C reduced the reaction time to 6−8 h with around 97% yield without increase in the content of dimer impurity **9**. Compound **9** being poorly soluble in most of the solvents posed great difficulty to eliminate it from **1**. We did a detailed study on this impurity and found that the dimer impurity **9** is formed in the reaction due to the presence of traces of **14** in **5**, which in turn reacts with the **4** to form impurity **9** (Scheme 3, path-I).

Based on our investigation we controlled the content of **14** in **5** well below 0.10% and again performed the reaction under similar conditions. Surprisingly, product still showed the content of dimer impurity **9** up to the level of 0.12−0.14%, indicating an alternative way of its formation in the reaction mass. It was presumed that the iloperidone (**1**) formed in the reaction mass may further react with **5** at a particular time to provide dimer impurity **9** (Scheme 3, path-II). Based upon experiential data, we noticed that the mole ratio of **5** also plays an important role for the formation of dimer impurity **9**, and hence, the mole ratio has been optimized to 1.02 mol with respect to **4**. However, we did not achieve substantial improvements with this parameter, as still the dimer impurity **9** appeared in the range of 0.11%. Further we explored biphasic reactions using water and water immiscible solvents such as dichloromethane, chloroform, toluene, hexane, and heptane for the preparation of **1**. Surprisingly, we observed that with the use of water and heptane mixture as a solvent and tetrabutylammonium bromide as a catalyst the formation of dimer impurity **9** was reduced to 0.04−0.06%. Further, it was also studied that the concentration of heptane plays a vital role in controlling the dimer impurity **9**. Water (10 volumes) and heptane (0.5 volumes) with respect to per gram of **4** as a solvent with sodium hydroxide as a base in the presence of tetrabutylammonium bromide as a catalyst at 65−70 °C for 6−8 h was found to be the best condition for this reaction. The completion of reaction was monitored by HPLC; after completion of reaction, the reaction mass was cooled to 25−30 °C and the product was extracted using dichloromethane. The dichloromethane layer containing product was washed with water and treated with activated carbon and finally concentrated under vacuum to obtain crude **1** with about 98% yield and at least around 97% purity by HPLC.

Of the nine possible potential impurities (Scheme 2), **4**, **5**, and **6** are the staring materials; impurity **8** was identified as desfluoro iloperidone, and its formation in the product was investigated. It was observed that the presence of trace amounts of **7** in **5** undergoes similar reaction along with **4** or **6** to generate **8** as an impurity in the **1**. Removal of **8** in **1** was difficult due to structural similarity to **1**. In order to have better control on **8**, the content of **7** in **5** was controlled by purification of **5**, and the limit of **7** in **5** was restricted to not more than 0.10% by HPLC (Scheme 1, Path B; Table 1). The

Table 1. Comparative Experimental Data of 8 in 1 by Using Varied Contents of 7 in 5

exp. no.	content of **7** in **5** (%)	content of **8** in **1** (%)
1	0.20	0.08
2	0.10	0.03
3	0.05	not detected

use of a stoichiometric amount of **5** with respect to **4** in the reaction controlled the level of **5** in **1**. A set of experiments are also conducted using **5** with various contents of **7** to evaluate the process capability to control **8** in **1** (Table 1).

Impurities **9** and **12** are identified as by-products formed in the reaction during the manufacturing of **1**. Impurity **10** was a carryover impurity from **4** and was controlled during synthesis of **4** by using an excess quantity of **3** during its condensation reaction with **2**. To have better control on **10**, we performed a few reactions with different mole ratios of **3** for the synthesis of **4**. Based on our experimental data, we found that a minimum of 3 mol of **3** was required per mole of **2** for the synthesis of **4**.[13] Impurity **11** was identified as iloperidone *N*-oxide, whose probability to be present in the product was low, and it was found to be a potential degradation product during forced degradation studies using hydrogen peroxide. Impurity **12** was identified as a byproduct formed in the reaction during the manufacturing of **1**. Since the synthesis of **1** is performed in aqueous alkaline medium, hence, during synthesis of **1**, fractions of **4** and **6** undergo hydrolysis, which leads to the formation of **12**. During synthesis of **1**, as per the reported process, the use of potassium carbonate as a base leads to formation of carbon dioxide as one of the side products, which further hinders the manufacturing process by actively participating in the process and thereby leading to the formation of carbamate impurity **13**. Thus, the formation of **13** was totally arrested with the use of sodium hydroxide as a base during the synthesis of **1**.

Crystallization of crude **1** was then explored using methanol, ethanol, isopropyl alcohol, acetone, methyl ethyl ketone, *n*-propanol, 1-butanol, isopropanol, 1-pentanol, tetrahydrofuran, 2-methyltetrahydrofuran, toluene, and their mixture with water. During the screening study of solvents, it was observed that isopropyl alcohol, with a volume of around 5 to 6 times with respect to crude **1** was found to be effective for purification of **1**. The content of impurities **8**, **9**, **11**, and **13** has been evaluated thoroughly by HPLC in the crude **1** to establish the purification efficiency, and the data are provided in Table 2.

■ CONCLUSIONS

This contribution presents an efficient, production friendly, commercially viable, and high-yielding process for the

dx.doi.org/10.1021/op400335p | *Org. Process Res. Dev.* 2014, 18, 342−348

Table 2. Content of Impurities in 1 at Different Stages of Manufacturing Process

		contents of impurities by HPLC (%)										
batch no.	particulas	4	5	6	8	9	10	11	12	13	1	SMU[b]
1	RM[a]	0.62	0.13	0.12	0.02	0.07	0.36	ND	0.08	ND	98.46	0.14
	crude 1	0.55	0.12	0.14	0.02	0.07	0.33	ND	0.07	ND	98.60	0.08
	pure 1	ND	ND	0.01	ND	0.04	0.02	ND	ND	ND	99.85	0.05

[a]RM = reaction mixture. [b]SMU = single maximum unknown impurity; ND = not detected.

production of iloperidone (**1**) which is substantially free from impurities and meets the regulatory norms in terms of quality and an overall yield of about 82% via phase transfer catalyzed *N*-alkylation of amine compound **5** with halide compound **4** in water and heptane mixture with sodium hydroxide as a base. The developed process was successfully implemented in the plant level with high production throughput.

EXPERIMENTAL SECTION

General. Melting points were determined on an Analab melting point apparatus, in open capillary tubes, and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 400 MHz FT NMR spectrometer. Chemical shifts were reported in parts per million using tetramethylsilane as internal standard and are given in δ units. The solvents for NMR spectra were deuterochloroform and deuterodimethylsulfoxide unless otherwise stated. Infrared spectra were taken on a Perkin-Elmer Spectrum 100 instrument in potassium bromide pellets unless otherwise stated. Elemental analyses were performed on a Hosli CH-Analyzer, and the results were within ±0.35% of the calculated values. High-resolution mass spectra were obtained with a Shimadzu GC-MS QP mass spectrometer with an ionization potential of 70 eV. All reactions were monitored by high-performance liquid chromatography (HPLC) on an Agilent Technologies 1200 series instrument. Gas chromatography on an Agilent Technologies 7683B instrument with head space was used for analyzing the residual solvents. The common reagent grade chemicals used were either commercially available and were used without further purification or were prepared by standard literature procedures.

Scale up Batch. *Synthesis of 1-[4-(3-Chloropropoxy)-3-methoxyphenyl] Ethanone (**4**).* Anhydrous *N*,*N*-dimethyl formamide (3.0 L) and 1-(4-hydroxy-3-methoxyphenyl)-ethanone (1.0 kg, 6 mol) were charged to the reactor and stirred to obtain a clear solution at 25−30 °C. To the obtained clear solution was charged anhydrous potassium carbonate (1.0 kg 7.23 mol), and the reaction mixture was stirred at 25−30 °C, and finally to the reaction mixture was charged 1-bromo-3-chloro propane (2.85 kg, 18.1 mol). The reaction mass was maintain at 25−30 °C for 8−10 h. The completion of reaction was monitored by HPLC. Upon completion of reaction, the reaction mass was quenched with water (30 L). To the obtained solution was added toluene (6 L), the mixture was stirred for 30 min, and layers were allowed to settle for 30 min. The toluene layer was separated from the aqueous phase. To the separated aqueous layer was added toluene (6 L), the mixture was stirred for 30 min, and layers were allowed to settle for 30 min. The toluene layer was separated from the aqueous phase. Finally both the toluene layers were combined, to this was added water (7 L), the mixture was stirred for 30 min, and the layers were allowed to settle for 30 min. The toluene layer was separated from the aqueous phase and was recharged with water (5 L), the mixture was stirred for 30 min, and the layers were allowed to settle for 30 min. The toluene layer was separated from the aqueous phase. The toluene layer was then subjected to distillation at 60−65 °C under vacuum. Once the distillation was completed, the obtained oil was degassed at 60−65 °C under vacuum for 60 min and cooled to 50 °C. The obtained oil was treated with toluene (1.4 L) and cyclohexane (7.4 L). The mixture was then heated to 58−60 °C for 30 min and then gradually cooled to 20−25 °C to obtain the precipitate. The precipitated product was then stirred at 20−25 °C for 30 min and then further cooled to 0−5 °C and stirred for 30 min. The precipitate obtained was filtered and washed with prechilled cyclohexane (1.4 L). The weight of wet product was 1.76 kg. The obtained wet cake was dried in a vacuum tray dryer at 40−45 °C for 6−8 h. The dry weight of **4** was 1.25 kg (85.6% yield); HPLC purity:[17] 98.83%, content of **10**: 0.45%; content of **6**: 0.70%. Single maximum unknown impurity: 0.02%; mp 61−63 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3072, 2964, 2933, 2842, 2878, 1670, 1596, 1587, 1523, 1515, 1466, 1452, 1420, 1355, 1277,1225, 1183, 1146, 1077, 1034, 873, 806, 757, 722; ^{1}H NMR ($CDCl_3$): δ 2.28−2.36 (m, 2H), 2.57 (s, 3H), 3.78 (t, 2H, J = 6.2 Hz), 3.91 (s, 3H), 4.24 (t, 2H, J = 6.0 Hz), 6.92 (d, 1H, J = 8.1 Hz), 7.53−7.58 (m, 1H), 7.53−7.58 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 25.82, 31.71, 41.08, 55.60, 65.11, 110.26, 111.23, 122.80, 130.36, 148.98, 152.20, 196.25; MS (ESI, m/z): 243 $[M + H]^+$.

*Synthesis of Iloperidone (**1**).* Water (10.0 L) and sodium hydroxide (0.5 kg 12.5 mol) were charged to the reactor, and the mixture was stirred to obtain a clear solution. The alkali solution was cool to 25−30 °C. 6-Fluoro-3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (**5**, 1.078 kg, 4.2 mol) was charged to the above prepared alkali solution and stirred for 15 min. To the reaction mixture was charged 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (**4**, 1.0 kg, 4.12 mol) at 25−30 °C, and the reaction misture was stirred for 15 min. Finally to the reaction mixture was charged *n*-heptane (0.5 L) followed by tetrabutylammonium bromide (1.0 g). The reaction mixture was then heated to 65−70 °C for 6−8 h.[16] Completion of the reaction was monitored by HPLC.[17] Upon completion of reaction, the reaction mass was cooled to 25−30 °C. To the reaction mixture was added dichloromethane (5 L), the mixture was stirred for 30 min, and the layers were allowed to settle for 30 min. Then the dichloromethane layer was separated from the aqueous phase. To the separated aqueous layer was added dichloromethane (5 L), and the mixture was stirred for 30 min, and the layers were allowed to settle for 30 min. The dichloromethane layers were combined, water (4 L) was added, and the mixture was stirred for 30 min. The layers were allowed to settle for 30 min. The dichloromethane layer was separated, treated with activated carbon (40 g), and stirred for 30 min. The dichloromethane layer was then filtered over a Celite bed, the bed was washed with dichloromethane (1.0 L), and the combined filtrate was subjected to distillation under vacuum to obtain the crude iloperidone (1.72 kg; 98% yield). The crude

dx.doi.org/10.1021/op400335p | Org. Process Res. Dev. 2014, 18, 342−348

iloperidone was treated with isopropyl alcohol (1.0 L) and stirred for 10−15 min. Isopropyl alcohol was distilled under vacuum at temperature not more than 55 °C to obtain the residue.[18] To the obtained residue was added isopropyl alcohol (9.7 L), and the mixture was heated to reflux temperature (80−85 °C) till clear solution was obtained. The obtained clear solution was gradually cooled to 25−30 °C and stirred for 60 min. The precipitate obtained was filtered and washed with isopropyl alcohol (1 L). Weight of wet product was 1.85 kg. Obtained wet product was dried under vacuum at 50−55 °C for 6−7 h. Dry weight of **1** was 1.68 kg (95% yield). HPLC purity:[17] 99.85%. FT-IR (KBr, λ_{max}, cm^{-1}): 3031, 2949, 2779, 2746, 2822, 1669, 1614, 1585, 1510, 1462, 1448, 1415, 1380, 1313, 1262, 1221, 1177, 1150, 1123, 1077, 1034, 997, 985, 955, 884, 876, 853, 812, 781, 643, 610, 569, 475. ^{1}H NMR ($CDCl_3$): δ 2.03−2.10 (m, 6H), 2.12−2.18 (m, 2H), 2.55−2.56 (s, 3H), 2.58−2.60 (t, 2H), 3.02−3.09 (m, 3H), 3.91 (s, 3H), 4.10−4.19 (t, 2H), 6.91−6.93 (d, 1H), 7.01−7.06 (dd, 1H), 7.21−7.24 (dd, 1H), 7.51−7.52 (d, 1H), 7.53−7.56 (dd, 1H), 7.69−7.65 (dd, 1H). ^{13}C NMR ($CDCl_3$): 26.02, 26.40, 30.36, 34.34, 53.36, 54.90, 55.80, 67.16, 97.04, 97.31, 110.20, 111.02, 111.98, 112.23, 117.12, 122.36, 122.46, 123.06, 130.11, 149.00, 152.66, 160.91, 162.60, 163.53, 163.66, 165.09, 198.59. MS (ESI, m/z): 427.2 $[M + H]^+$. Anal. Calcd (%) for $C_{24}H_{27}FN_2O_4$ (426.48): C, 67.54; H, 6.33; found (%): C, 67.24; H, 6.18.

Synthesis of Related Substances. *Synthesis of 1-[4-(3-Bromopropoxy)-3-methoxyphenyl]ethanone (**6**).* To a stirred solution of 1-(4-hydroxy-3-methoxyphenyl)ethanone (**2**) (15 g, 90 mmol) were charged *N*,*N*-dimethylformamide (50 mL), potassium carbonate (15 g, 108 mmol), and 1,3-dibromopropane (**3**) (55 g, 272 mmol) at 25−30 °C. The reaction mixture was then maintained at 25−30 °C for 8−10 h. Progress of the reaction was monitored by HPLC; after completion of the reaction, the reaction mixture was quenched with water (500 mL) and product was extracted twice with toluene (150 mL). The combined toluene layers were washed twice with water (125 mL). The toluene layer was concentrated By rotary evaporation to obtain a residue (15 g). The obtained residue was purified by column chromatography using 3% ethyl acetate in heptane. The fractions containing the desired product were combined and concentrated to obtain a solid which was finally crystallized from cyclohexane (125 mL) to obtain pure **6** (8 g). HPLC purity:[17] 99.6%; FT-IR (KBr, λ_{max}, cm^{-1}): 3073, 3008, 2958, 2932, 2841, 1669, 1595, 1586, 1521, 1466, 1448, 1419, 1383, 1350, 1274, 1224, 1182, 1145, 1039, 1022, 873, 807; ^{1}H NMR ($CDCl_3$): δ 2.36−2.45 (m, 2H), 2.57 (s, 3H), 3.63 (t, 2H, J = 6.3 Hz), 3.91 (s, 3H), 4.23 (t, 2H, J = 5.9 Hz), 6.92 (d, 1H, J = 8.4 Hz), 7.53−7.58 (m, 1H), 7.53−7.58 (m, 1H); MS (ESI, m/z): 287 $[M + H]^+$.

*Synthesis of 1,1′-{Propane-1,3-diylbis[oxy(3-methoxy-4,1-phenylene)]} Diethanone (**10**).* To a stirred solution of 1-(4-hydroxy-3-methoxyphenyl) ethanone (**2**) (20 g, 120 mmol), *N*,*N*-dimethyl formamide (200 mL), and potassium carbonate (32 g, 232 mmol) was charged 1-[4-(3-chloropropoxy)-3-methoxyphenyl] ethanone (**4**) (29.3 g, 120 mmol) at 25−30 °C. The reaction mixture was then stirred for 2 h at 25−30 °C, and then the temperature of the reaction mass was raised to 70−75 °C and maintained for 18−20 h. The progress of the reaction was monitored by TLC (heptane:ethyl acetate; 4:6); after completion of reaction, it was cooled to room temperature and quenched with water (200 mL). The desired product was extracted twice using dichloromethane (150 mL). Finally the combined dichloromethane layer was washed twice with water (200 mL). The dichloromethane layer was then concentrated by rotary evaporation to obtain a residue (35 g). To the obtained residue was added isopropyl alcohol (400 mL), and the mixture was refluxed for 25 min. Finally the mixture was cooled to 0−5 °C and stirred for 60 min. The precipitated product was filtered under suction and washed with isopropyl alcohol (20 mL). The obtained wet material (30 g) was dried under vacuum at 50−55 °C to furnish **10** (28 g). HPLC purity:[17] 99.85%; FT-IR (KBr, λ_{max}, cm^{-1}): 3081, 2958, 2938, 1671, 1586, 1513, 1462, 1450, 1417, 1345, 1273, 1220, 1147, 1050, 1031, 1022, 875, 807, 795; ^{1}H NMR ($CDCl_3$): δ 2.38−2.46 (m, 2H), 2.56 (s, 6H), 3.91 (s, 6H), 4.32 (t, 4H, J = 6.2 Hz), 6.94 (d, 2H, J = 8.1 Hz), 7.53−7.56 (m, 2H), 7.53−7.56 (m, 2H); MS (ESI, m/z): 373 $[M + H]^+$.

*Synthesis of 1-[3-(4-Acetyl-2-methoxyphenoxy)propyl]-4-(6-fluorobenzo[d]isoxazol-3-yl) Piperidine 1-Oxide (**11**).* Iloperidone (**1**; 10 g, 23 mmol) was charged to 30% hydrogen peroxide (170 mL) and stirred for 30 min at 25−30 °C, and then the temperature of the reaction mass was raised to 40−45 °C and maintained for 70−75 h. The progress of the reaction was monitored by TLC (ethyl acetate/toluene/acetone; 2:6:2); after completion of reaction, it was cooled to 0−5 °C and the reaction mass was basified to pH between 8 and 9. The obtained precipitate was stirred for 30 min at 0−5 °C and filtered. The obtained wet material was dried under vacuum at 50−55 °C to furnish crude **9**. The obtained crude product was recrystallized from isopropyl alcohol thrice to yield white solid **11** (1.5 g). HPLC purity:[17] 98.27%; FT-IR (KBr, λ_{max}, cm^{-1}): 3083, 2958, 2878, 1655, 1606, 1584, 1509, 1467, 1419, 1348, 1273, 1223, 1182, 1143, 1121, 1032, 971, 957, 881, 857, 813, 802; ^{1}H NMR ($CDCl_3$): δ 1.89−1.93 (m, 2H), 2.31−2.40 (m, 2H), 2.55 (s, 3H), 2.60−2.72 (m, 2H), 3.29−3.52 (m, 2H), 3.29−3.52 (m, 2H), 3.29−3.52 (m, 2H), 3.29−3.52 (m, 1H), 3.85 (s, 3H), 4.23 (t, 2H, J = 6.0 Hz), 7.11 (d, 1H, J = 8.4 Hz), 7.30−7.36 (m, 1H), 7.62−7.65 (m, 1H), 7.71−7.74 (dd, J = 9.3 and 2.0 Hz, 1H), 8.02−8.07 (dd, J = 8.7 and 5.4 Hz, 1H); MS (ESI, m/z): 443 $[M + H]^+$.

*Synthesis of 1-[4-(3-Hydroxypropoxy)-3-methoxyphenyl]-ethanone (**12**).* To a stirred solution of 1-(4-hydroxy-3-methoxyphenyl)ethanone **2** (10 g, 60 mmol), acetonitrile (100 mL), and potassium carbonate (20.8 g, 150 mmol) was charged 3-bromopropan-1-ol (17 g 122 mmol) at room temperature. The reaction temperature was raised to 60−65 °C and maintained for 26−28 h. The progress of the reaction was monitored by TLC (chloroform/methanol, 9.5:0.5). Upon completion of reaction, the reaction mixture was cooled to room temperature and filtered. The obtained filtrate was concentrated by rotary evaporation to obtain a residue that was finally recrystallized from toluene to furnish pure **12** (15 g). HPLC purity:[17] 98.88%; FT-IR (KBr, λ_{max}, cm^{-1}): 3011, 2955, 2923, 2842, 1663, 1590, 1552, 1501, 1470, 1422, 1349, 1262, 1211, 1175, 1143, 1075, 1043, 852, 806, 762, 721; ^{1}H NMR ($CDCl_3$) δ 2.13−2.18 (m, 2H), 2.55 (s, 3H), 3.78 (t, 2H, J = 6.2 Hz), 3.91 (s, 3H), 4.25 (t, 2H, J = 6.0 Hz), 4.39 (t, 1H, J = 6.8 Hz), 6.92 (d, 1H, J = 8.1 Hz), 7.53−7.58 (m, 1H), 7.53−7.58 (m, 1H); MS (ESI, m/z): 225 $[M + H]^+$.

*Synthesis of 3-(4-Acetyl-2-methoxyphenoxy)propyl-4-(6-fluorobenzo[d]isoxazol-3-yl) Piperidine-1-carboxylate (**13**).* To a stirred solution of 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (**4**, 20 g, 82.5 mmol), *N*,*N*-dimethyl formamide (240 mL), and potassium carbonate (28.5 g, 206 mmol) was charged 6-fluoro-3-piperidin-4-yl-1,2 benzisoxazole hydrochloride (**5**, 24.3 g, 94.74 mmol) at 25−30 °C. The

dx.doi.org/10.1021/op400335p | *Org. Process Res. Dev.* 2014, 18, 342−348

reaction mixture was then stirred for 2 h at 25−30 °C, and then the temperature of the reaction mass was raised to 110 °C and maintained for 18−20 h. The progress of the reaction was monitored by HPLC after completion of the reaction, the reaction mixture was cooled to room temperature, and the reaction was quenched with water (500 mL). The desired product was extracted twice using dichloromethane (250 mL). Finally the combined dichloromethane layer was washed twice with water (200 mL). The dichloromethane layer was then concentrated by rotary evaporation to obtain a residue (12.5 g). The obtained residue was purified by column chromatography using 3% ethyl acetate in heptane to furnish crude **13** (8 g) with an HPLC purity of 82.0%. The crude product was further purified by column chromatography as mentioned above to furnish semipure **13** with an HPLC purity of 88.3%. Semipure **13** was crystallized from ethanol to obtain pure **13** (1 g). HPLC purity:[17] 96.80%; FT-IR (KBr, λ_{max}, cm^{-1}): 470.6, 569.0, 642.3, 804.3, 956.7, 1031.9, 1099.5, 1122.6, 1220.9, 1263.4, 1350.2, 1415.8, 1512.2, 1591.3, 1612.5, 1680.1, 1695.5, 2852.8, 2924.2, 2960.8, and 3076.6 cm^{-1}. ^1H NMR ($CDC1_3$): δ 1.880 (m, 2H), 1.996 (m, 2H), 2.206 (m, 2H), 2.518 (s, 3H), 2.999 (t, 2H), 3.216 (m, lH), 3.860 (s, 3H), 4.262 (m, 6H), 6.860 (d, lH), 7.026 (t, lH), 7.219 (t, lH), 7.488 (m, 2H), and 7.589 (m, lH); LCMS (ESI, m/z): 471.02 $[M + H]^+$.

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Funding

†Megafine Publication Number: MF/015/2013.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors are grateful to Mr. Shailesh Sanghvi, Mr. Hasmukh Gandhi, and Mr. Ashok Jhaveri, Directors of Megafine Pharmaceuticals (P) Ltd., for encouraging this work. We also appreciate and thank the colleagues of Analytical Research and Development Department, Megafine Pharmaceuticals (P) Ltd., for valuable support and cooperation in developing the chromatographic methods for establishing the process and identifying the impurities.

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(16) During the progress of the reaction at 65−70 °C, iloperidone is precipitated out from clear solution after around 2−3 h. If required, product can be filtered at 25−30 °C as a crude solid API after completion of reaction. Since authors wanted to avoid the filtration and drying of the crude to reduce the time cycle and increase the throughput in the production, dichloromethane was added to the reaction mass and extracted the crude API, which was subsequently purified with IPA without isolation. Drying of the crude was necessary prior to IPA purification to achieve the right quality and yield.

(17) Related substances and assay of iloperidone were estimated by gradient HPLC analysis developed at Megafine using a Hypersil BDS C18 column (250 mm × 4.6 mm, particle size 5 μm); mobile phase A comprising a mixture of 5.0 mM ammonium dihydrogen orthophosphate buffer and 0.1% triethylamine; mobile phase B comprising a mixture of acetonitrile/methanol in the ratio 80:20 v/v; gradient elution: time (min)/A (v/v): B (v/v); T0.01/65:35, T8.0/65:35, T25.0/35:65, T35.0/35:65, T37.0/65:35, T45.0/65:35; flow rate 1.0 mL/min; column temperature 30 °C; wavelength 225 nm. The observed retention time of iloperidone under these chromatographic conditions is about 17.0 min. The analytical method developed is capable of detecting the tetrabutylammonium bromide (TBABr). However, tetrabutylammonium bromide was not detected in the API.

(18) IPA distillation was performed to remove the traces of dichloromethane completely from the crude **1**, as its presence leads to the low yields due to the higher solubility of API in dichloromethane.