Organic Process Research & Development

Article

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Investigational Study into the Formation of Methoxy Derivative and Other Impurities during the Optimization of Eletriptan Hydrobromide

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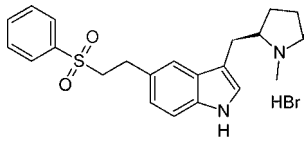
ABSTRACT: During the process development of eletriptan hydrobromide, we have observed formation of an unknown impurity in the final product at enhanced levels which was identified as a methoxy substituted derivative on the side chain of the product. The present work involves detailed optimization studies directed toward the development of an efficient process for the commercial production of eletriptan hydrobromide substantially free from the methoxy impurity and other impurities.

INTRODUCTION

Eletriptan Hydrobromide (trade name Relpax) is a selective agonist of 5-HT_1-receptors and particularly of 5-$HT_{1B/1D}$ receptors and is widely used as an antimigraine agent.[1−4] It is chemically known as (*R*)-3-[(1-methyl-2-pyrrolidinyl)methyl]-5-[2-(phenylsulphonyl)ethyl]-1H-indole hydrobromide, which may be represented by chemical formula **5**.



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Although there are several methods reported in the literature for the synthesis for eletriptan hydrobromide,[5−8] we considered Scheme 1 for the development based on the commercial availability of raw materials and the scale-up suitability. The scheme involves reaction of (*R*)-1-acetyl-5-(phenylsulfonylethenyl)-3-(*N*-methylpyrrolidin-2-ylmethyl)-1*H*-indole **2** by means of K_2CO_3 in methanol at ambient temperature, yielding (*R*)-5-(phenylsulfonylethenyl)-3-(*N*-methylpyrrolidin-2-ylmethyl)-1*H*-indole (**3**), reducing the C═C double bond in the presence of Pd/C to give (*R*)-5-(phenylsulfonylethyl)-3-(*N*-methylpyrrolidin-2-ylmethyl)-1*H*-indole (**4**), which affords eletriptan hydrobromide by treating with aqueous hydrobromic acid. The above process was studied to optimize various process parameters in the laboratory and finally made suitable for scale-up in a commercial plant. Herein we report our investigation on the role of solvent systems, reagents, and temperature on the rate of reaction and impurity profile of the final product.

RESULTS AND DISCUSSION

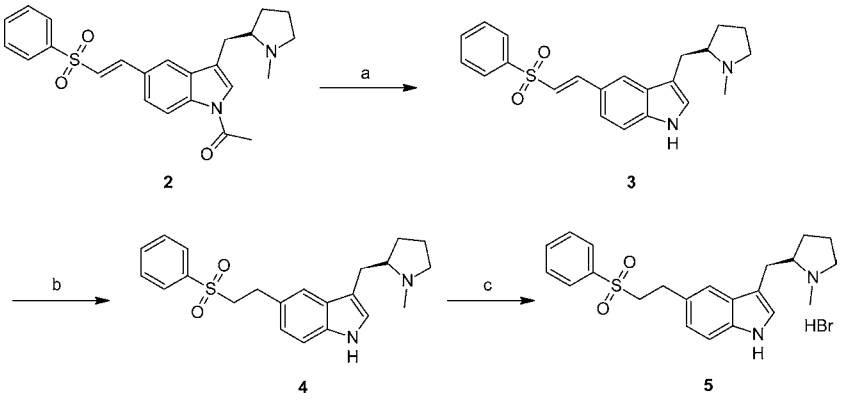
Key intermediate **2** was prepared on the basis of a reported procedure[5] by the Heck reaction (Scheme 2) of (*R*)-1-acetyl-5-bromo-3-(*N*-methylpyrrolidin-2-ylmethyl)-1*H*-indole (**1**) and phenyl vinyl sulfone in the presence of palladium acetate and tri(*o*-tolyl) phosphine. Hydrolysis of **2** was performed with potassium carbonate and methanol as solvent at ambient temperature to afford (*R*)-5-(phenylsulfonylethenyl)-3-(*N*-methylpyrrolidin-2-ylmethyl)-1*H*-indole (**3**). Intermediate **3** was subjected to catalytic hydrogenation, followed by the addition of hydrobromic acid to obtain eletriptan hydrobromide (**5**).

During our preliminary optimization studies, we have observed four major impurities in the final product, and the molecular weights of these impurities were identified by LC−MS analysis as 242, 380, 398, and 412, of which the impurities with molecular weight 242, 380, and 398 were identified as 5-ethyl-3-(*N*-methylpyrrolidin-2-ylmethyl)-1H-indole (**6**), unreduced intermediate **3**, and *N*-oxide derivative **7**, respectively, with the available literature.[9,10] The structure was further confirmed through synthesis/isolation from mother liquor, characterization, and HPLC spike studies. The content of **3**, **6**, and **7** in the final product varied depending upon the various process parameters of the reduction and salt formation steps, and the control of these impurities could be accomplished by employing appropriate controls in the process and solvents used in the process. On the other hand, to our surprise, the content of impurity with the molecular weight 412 remains unchanged by varying the process parameters in the reduction step. Detailed investigation and careful mapping of the impurities at all the stages indicated that the impurity was formed during the penultimate hydrolysis step due to 1,4 addition of methanol to the α,β-unsaturated sulfone in the presence of base.[11] The structure of the impurity is thus identified as methoxy derivative **8** and further confirmed by its synthesis, characterization, and HPLC spike studies. Despite our sincere investigations on various parameters to remove impurity **8** during the isolation of intermediate **3**, reduction, salt formation, and subsequent purification of final product, the content of impurity **8** was the same or marginally reduced and often resulted in undesirable quality of the product with poor yield; hence, it is essential to control this impurity at the hydrolysis stage by optimizing the process conditions.

Received: September 5, 2012
Published: November 5, 2012

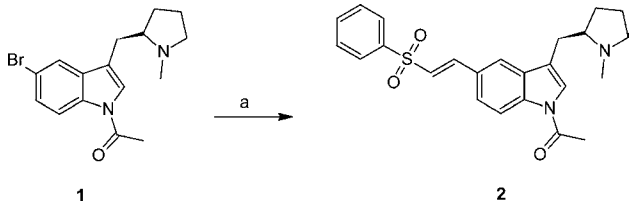
dx.doi.org/10.1021/op3002454 | *Org. Process Res. Dev.* 2012, 16, 1917−1920

Scheme 1[a]



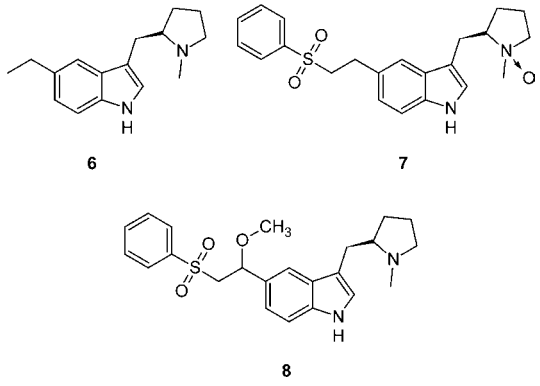
[a]Reaction conditions: (a) methanol/water, K_2CO_3; (b) acetone/water, $MeSO_3H$, H_2, Pd/C 5%; (c) IPA, aqueous hydrobromic acid (48%).

Scheme 2[a]



[a]Reaction conditions: (a) DMF, $Pd(OAc)_2$/tri-*o*-tolyl phosphine, triethylamine, phenyl vinyl sulfone.

During the optimization of the process parameters of the hydrolysis step, initially we studied various solvents systems such as, methanol/water, THF/water, and isopropyl alcohol for the reaction, of which the methanol/water solvent system is found to be the better choice for this reaction on the basis of the conversion and operational ease during work up. Temperature and nature of base were observed to be most critical for the formation of the methoxy impurity; hence, the use of stronger bases such as sodium hydroxide, potassium carbonate, and higher temperature was detrimental during the reaction and led to formation of impurity to the level of more than 25% (entries 3, 4, and 5, Table 1). Lower temperature and milder base, such as sodium bicarbonate, are the preferred choice of conditions, which resulted in a substantially lower level of impurity formation (entries 9 and 10, Table 1). Table 1 summarizes the impact of various factors, such as solvent, base, and temperature, on the content of methoxy impurity **8**.



After achieving appropriate controls on the formation of **8**, our attention turned to containing the level of impurities of **3**, **7**, and **6** in the final product. During the course of our optimization study on various work up procedures and solvent purifications of final product to minimize the level of these impurities, we observed that the content of unreduced intermediate **3** and impurity **7** is unchanged, akin to the case of impurity **8**, but the level of impurity **6** is reduced to less than 0.1% from 1.0% by HPLC. It was a challenging task to control the level of unreduced intermediate **3** and impurity **6**, since milder reduction conditions resulted in incomplete conversion

Table 1. Effect of Solvent, Base, and Temperature on the Content of Impurity 8 during Hydrolysis of Intermediate 2

					HPLC purity	
entry	solvent	base	mole[a]	reaction temp (°C)	impurity **8** (%)	intermediate **3** (%)
1	isopropyl alcohol	K_2CO_3	1.0	25−35		no reaction
2	THF/water (8:2)	K_2CO_3	1.0	25−35		no reaction
3	methanol	NaOH	2.0	60−65	42.30	52.65
4	isopropyl alcohol	K_2CO_3	1.0	60−65	26.36	53.49
5	methanol/water (5:2)	K_2CO_3	2.5	60−65	42.5	53.9
6	methanol/water (9:1)	K_2CO_3	1.0	45−50	9.03	90.4
7	methanol/water (9:1)	K_2CO_3	0.5	25−35	1.13	96.78
8	methanol/water (9:1)	K_2CO_3	0.3	25−35	0.45	97.61
9	methanol/water (9:1)	$NaHCO_3$	1.0	25−35	ND	99.83
10	methanol/water (9:1)	$NaHCO_3$	1.0	40−50	ND	99.83

[a]As part of our process optimization, we studied the impact of mole ratio of base in a particular solvent system on the formation of methoxy derivative and observed it to be higher if the amount of base used is higher and vice versa.

dx.doi.org/10.1021/op3002454 | *Org. Process Res. Dev.* 2012, 16, 1917−1920

Table 2. Effect of Solvent Ratio and Acid Catalyst in the Formation of 6 during Hydrogenation of 3

						HPLC purity (%)		
entry	solvent	acid catalyst	mol of acid	H_2(g) pressure (atm)	time	3	4	6
1	MeOH (90%) water (10%)	AcOH	1.2	5.0	6 h	0.04	91.54	6.68
2	MeOH (90%) water (10%)	MsOH	1.2	5.0	10 h	1.88	94.94	1.01
3	acetone	MsOH	1.5	5.0	9 h	7.15	90.32	0.47
4	acetone (90%) water (10%)	AcOH	1.2	5.0	8 h	0.04	92.57	5.14
5	acetone (90%) water (10%)	MsOH	1.1	5.0	10 h	0.01	94.01	4.74
6	acetone (90%) water (10%)	MsOH	1.2	5.0	3 h	0.04	96.61	1.04
7	acetone (90%) water (10%)	MsOH	1.5	5.0	2 h	0.01	97.02	0.91
8	acetone (90%) water (10%)	MsOH	1.5	5.0	2 h	0.05	97.54	0.82
7	acetone (90%) water (10%)	MsOH	2.0	5.0	2 h	0.01	97.53	0.71

and rigorous conditions resulted in the formation of an enhanced level of impurity **6**. However, by carrying out several optimizing experiments and the reduction conditions available in the literature,[12,13] we could identify that the nature and mole ratio of acid used were the most critical parameters; hence, use of stronger acid and excess moles of acid during the reaction could complete the reaction in 2.0 h with the desired profile of impurity **6** and **3** to a level of <1% and <0.1%, respectively (entries 7, 8, and 9, Table 2). Weaker acids and lower mole ratio of acid resulted in poor rate of conversion and undesired impurity profile (entries 4 and 5, Table 2). Although the other stronger inorganic acids such as hydrochloric acid gave a similar result to that of methanesulfonic acid during our optimization studies, inorganic acids were not considered because of the corrosive nature and operational issues related to handling during scale up. A combination of acetone (90%), water (10%), and methanesulfonic acid (1.5 mol), under a hydrogen pressure of 5 atm, was observed to be the optimal conditions for the reaction. Table 2 briefly summarizes our efforts in arriving at the proper combination of process parameters to obtain the desired levels of **3** and **6** in the final product. Finally, the formation **7** could be controlled by avoiding oxidizing conditions during the reaction, work up, and crystallization and ensured the preparation of eletriptan hydrobromide of pharmaceutically acceptable quality in good yield.

CONCLUSION

We have demonstrated, through a detailed investigation, the chemistry of formation of methoxy impurity and other impurities, which prompted us to identify proper conditions for reactions, thereby controlling the impurity formation and avoiding costly purifications at later stages. This allowed us to develop an optimal process to prepare eletriptan hydrobromide, which can be scaled up in a commercial plant.

EXPERIMENTAL SECTION

General Procedures. Commercially available solvents and reagents were used without further purification. Reversed phased HPLC elutions were performed on a stainless steel column (250 mm length, 4.6 mm internal diameter, and filled with porous silica particles of 5 μm diameter, which are bonded to cyanopropyl group) using acetonitrile and buffer (2.72 g of potassium dihydrogen orthophosphate in 1.0 L of water and adjust pH 3.0 with ortho phosphoric acid) mixtures. ^{1}H NMR spectra were recorded on a Bruker Avance 400 MHz spectrophotometer with a multinuclear BBO probe with TMS as internal standard in DMSO-d_6/$CDCl_3$. Chemical shifts are reported in δ scale (ppm). Mass spectra were measured on a PE-SCIEX API-3000 LC/MS/MS with a Turbo ion spray mass spectrophotometer. IR spectra were recorded on a Perkin-Elmer spectrum 65 FT-IR spectrophotometer in KBr pellets.

(*R*)-1-Acetyl-5-bromo-3-(*N*-methylpyrrolidin-2ylmethyl)-1*H*-indole (1). A suspension of (*R*)-5-bromo-3-(*N*-methylpyrrolidin-2ylmethyl)-1*H*-indole (200 g, 0.68 mol) in toluene (1000 mL) containing triethylamine (104 g, 1.03 mol) and 4-dimethylaminopyridine (4.19 g, 0.034 mol) was treated with acetic anhydride (122 g, 1.20 mol) over 15 min, and then the mixture was heated to 105−115 °C and maintained for 5−6 h. The mixture was allowed to cool and was quenched with aqueous bicarbonate solution. The phases were separated, and the organic phase was washed with water before evaporating under vacuum to afford 218 g of oil, a 95% yield of **1**.

(*R*)-1-Acetyl-5-(phenylsulfonylethenyl)-3-(*N*-methylpyrrolidin-2ylmethyl)-1*H*-indole (2). To the above obtained oil (218 g, 0.65 mol) was added dimethylformamide (400 mL), and the reaction mixture was stirred at 25−35 °C to give a clear solution. This solution was added to a solution of palladium acetate (2.99 g, 0.0133 mol), tri-*o*-tolyl phosphine (18.2 g, 0.0597 mol), phenyl vinyl sulfone (126.74 g, 0.7534 mol), and triethylamine (139 g, 1.38 mol) in dimethylformamide (400 mL) over 15 min, and then the mixture was heated to 100−120 °C. The mixture was maintained for 5−6 h, was allowed to cool, and was filtered. The filtrate was diluted with water and acetone to obtain a dark brown slurry. The mixture was filtered, and the crude solid was washed with water. The crude wet solid was then purified with aqueous acetone and dried under vacuum to afford 200 g, 69% yield of **2**.

(*R*)-5-(Phenylsulfonylethenyl)-3-(*N*-methylpyrrolidin-2-ylmethyl)-1*H*-indole (3). A suspension of (*R*)-1-acetyl-5-(phenylsulfonylethenyl)-3-(*N*-methylpyrrolidin-2ylmethyl)-1*H*-indole (**2**) (80.0 g, 0.189 mol) in methanol/water (640 mL/80 mL) was treated with sodium bicarbonate (15.9 g, 0.189 mol) and heated to 40−50 °C. The reaction mass was maintained at 40−50 °C for 2−3 h and cooled to ambient temperature. The reaction mixture was stirred for 60 min after the addition of activated carbon (16.0 g). The reaction mass was filtered, and the residue was washed with methanol. The filtrate was diluted with water to obtain a pale brown slurry, and the solid was filtered. The solid was washed with water before drying under vacuum to give 62 g, 86% yield of **3**.

(*R*)-5-(Phenylsulfonylethyl)-3-(*N*-methylpyrrolidin-2-ylmethyl)-1*H*-indole (4). A solution of (*R*)-5-(phenylsulfonylethenyl)-3-(*N*-methylpyrrolidin-2-ylmethyl)-1*H*-indole (**3**) (27 g, 0.071 mol) in acetone (243 mL) and water (27 mL) was treated with methanesulfonic acid (10.21 g, 0.106 mol) at 25−30 °C over 5 min and then charged to a hydrogenator vessel. The mixture was hydrogenated at 5−6 atm hydrogen pressure and 25−35 °C in the presence of Pd/C 5% (50% wet)

dx.doi.org/10.1021/op3002454 | *Org. Process Res. Dev.* 2012, 16, 1917−1920

for 2−4 h. The reaction mass was filtered, and then acetone was removed completely under vacuum to obtain a reddish brown oil as a residue. The oil was dissolved in ethyl acetate, and water was added to the solution. The mixture was basified with 14% aqueous ammonia solution, and the phases were separated. The organic phase was washed with water, and the solvent was evaporated under vacuum to afford 25 g of oil, 92% yield of **4**.

(*R*)-5-(Phenylsulfonylethyl)-3-(*N*-methylpyrrolidin-2-ylmethyl)-1*H*-indole Hydrobromide Salt (5). A solution of (*R*)-5-(phenylsulfonylethyl)-3-(*N*-methylpyrrolidin-2-ylmethyl)-1*H*-indole (**4**) (25 g, 0.065 mol) in isopropyl alcohol (270 mL) was treated with 47% aqueous hydrobromic acid solution (11.62 g, 0.067 mol) at 25−35 °C and stirred for 4−5 h to obtain a pale brown slurry. The solid was filtered and washed with isopropyl alcohol to give 22 g of crude eletriptan hydrobromide (**5**). The crude obtained was purified with methanol and isopropyl alcohol to afford 20 g of pale brown solid, 66% of pure **5**.

5-Ethyl-3-{[1-methylpyrrolidin-2-yl]methyl}-1*H*-indole (6). The reaction mass obtained by the reaction conditions described in entry 6, Table 2 was worked up by following the procedure described above to isolate eletriptan hydrobromide (**5**). The mother liquor obtained was evaporated to obtain a crude product enriched with **6**. The crude product was purified by preparative HPLC to afford pure **6**. ^{1}H NMR (DMSO-d_6) δ: 1.2 (t, 3H), 1.46 (m, 1H), 1.58 (m, 2H), 1.70 (m, 1H), 2.16 (m, 1H), 2.38 (s, 3H), 2.41 (m, 1H), 2.45 (m, 1H), 2.64 (q, 2H), 3.02 (m, 2H), 6.91 (d, 1H), 7.09 (s, 1H), 7.22 (d, 1H), 7.29 (s, 1H), 10.6 (br s, 1H). m/z 243 $[M + H]^+$.

5-[1-Methoxy-2-(phenylsulfonyl)ethyl]-3-{[1-methylpyrrolidin-2-yl]methyl}-1*H*-indole (8). The reaction mixture obtained by the reaction conditions described in entry **3**, Table 1 was evaporated under vacuum to remove the solvent. The residue obtained was phased between dichloromethane and water. The organic phase obtained was evaporated under vacuum to afford the crude product. The crude product was purified by preparative HPLC to obtain pure **8**. ^{1}H NMR (DMSO-d_6) δ: 1.42 (m, 1H), 1.57 (m, 2H), 1.68 (m, 1H), 2.07 (m, 1H), 2.34 (m, 4H), 2.43 (m, 1H), 2.89 (s, 3H), 2.99 (m, 2H), 3.46 (m, 1H), 3.95 (m, 1H), 4.62 (m, 1H), 6.95 (d, 1H), 7.14 (d, 1H), 7.25 (d, 1H), 7.39 (s, 1H), 7.60 (t, 2H), 7.68 (t, 1H), 7.89 (d, 2H), 10.82 (br s, 1H). m/z 413 $[M + H]^+$.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank our management and the Analytical Research Department and IPM groups of Orchid Chemicals and Pharmaceuticals for their generous support. Finally, it is our pleasure to acknowledge the reviewers for their suggestions.

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