ISSN: 0974 - 7516 Volume 7 Issue 2

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Short Communication

OCAIJ, 7(2), 2011 [120-122]

A novel process for preparing substantially pure palonosetron hydrochloride, a 5-hydroxytryptamine subtype 3 receptor antagonist

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Received: 14th September, 2010 ; Accepted: 24th September, 2010

ABSTRACT

A novel process for preparing pure Palonosetron hydrochloride **(1)**, a 5-hydroxytryptamine subtype 3 receptor antagonist[1] is described. The new process is practical and commercially viable. The prior methods reported for preparing pure Palonosetron hydrochloride **(1)**, are cumbersome like in few instances involving repetition of a chemical conversion step and in some instances involving repeated crystallization to reach to the right diastereomerically pure product, thus making the synthetic process practically less viable and less economical. The new method as developed by us provides a novel way to prepare pure palonosetron hydrochloride **(1)**, by introducing catalytic amount of a suitable halogenating compound such as n-bromosuccinimide in the purification process which not only reduces the purification steps but also makes the process practical, robust and commercially viable. © 2011 Trade Science Inc. - INDIA

KEYWORDS

Palonosetron hydrochloride;
Diastereomers;
Allylic halogenation;
Crystallization.

INTRODUCTION

Palonosetron hydrochloride **(1)**[2], innovated by Syntex U.S.A., is available under the brand name Aloxi. It is a 5-hydroxytryptamine (serotonin) subtype 3 receptor antagonist having little or no affinity for other bioreceptors, including other serotonergic receptors 5-HT_1, 5-HT_2 and 5-HT_4. It is used in the prevention of acute as well as delayed nausea and vomiting associated with initial and repeat course of moderately and highly emetogenic cancer chemotherapy.

Several methods for preparing **(1)** are reported in literature[3]. In all the disclosures including patents and publications described in reference 3 as has been referred and used by the innovators also the most commonly employed procedure to provide pure palonosetron hydrochloride **(1)**, involves the catalytic reduction of intermediate **(2)** to provide diastereomeric palonosetrons **(3)** followed by its repetitive crystallization as such or as its hydrochloride **(3a)** from a suitable organic solvent mostly ethanol. The main drawback of all the reported procedures lies in the cumbersome methodology of repetitive crystallization to produce pure **(1)**, which not only leads to increased number of operations but also to a low yield of **(1)**. Also after the catalytic reduction of intermediate **(2)** the obtained intermediate **(3)** is always contaminated with varying amounts of unreacted **(2)** and no published literature to our knowledge teaches the removal of this unreacted **(2)**. Thus this commonly employed procedure to pre-

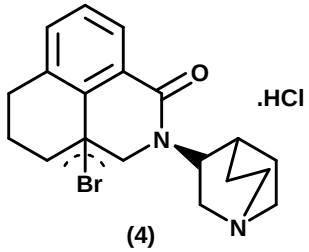
pare pure **(1)** does not always guarantee a consistency in terms of yield and quality.

Thus, the success of any process to synthesize **(1)** in a considerable yield and quality in a reproducible, practical and commercial manner would depend on the potential to (i) provide a simple methodology to remove the unreacted **(2)** from the prepared **(3)** and (ii) to avoid the cumbersome repetitive crystallization of the so obtained pure **(3)** or **(3a)** (substantially free from intermediate ii) to provide pure **(1)**. The hallmarks of this novel process is that it not only removes the unreacted **(2)** present in the reduced intermediate **(3)** but also provides pure **(1)** in one or two crystallization steps performed subsequently.

RESULTS AND DISCUSSION

Studies on improving the process to produce pure **(1)** to overcome the obvious drawbacks of the reported prior art was approached systematically in two stages. First stage of improvement was focused on the long standing problem of removing the varying amounts of unreacted **(2)** present as a contamination in intermediate **(3)** prepared by the catalytic reduction of **(2)** under pressure. Since repetitive crystallization by way of reported references were not viable we attempted to remove the unreacted **(2)** by way of its allylic halogenation by using a suitable halogenating agent in catalytic amounts in the crystallization medium. Initially the experiments were performed with 10 mol % of liquid bromine and liquid bromine-triphenylphosphine without much success. However when n-bromosuccinimide was used with or without free radical initiator under acidic conditions it was surprisingly observed that it could reduce or remove drastically the content of intermediate **(2)** present in isolated **(3)**. The amount of n-bromosuccinimide to be used was decided on the actual content of intermediate **(2)** present in the isolated **(3)** determined by HPLC analysis.

The next stage of improvement was purifying the so obtained **(3)** or **(3a)** (substantially free from 2) to pure **(1)**. It was observed that during the n-bromosuccinimide treatment as discussed above itself there was considerable enrichment of the desired (3a S,S)-diastereomer in the isolated **(3a)** hence one or



(4)

Figure 1 : Brominated derivative

two crystallization of the obtained **(3a)** in 5% methanol in ethanol lead to pure palonosetron hydrochloride **(1)**. The developed[1] methodology is depicted in Scheme 1. Also this methodology was found to be repeatable on different scales implying applicability in process validation of any type.

Though we at our end were not successful to isolate the halogenated product of intermediate **(2)** it is assumed that the unreacted **(2)** is eliminated as the proposed brominated derivative **(4)** (Figure 1) which is more soluble in the reaction system and is eliminated into the mother liqours.

EXPERIMENTAL

General

All materials were purchased from commercial suppliers and used without further purification. HPLC analyses were performed using Waters Alliance 2659 HPLC systems on a 4.6 x 250 mm, 5um, Zorbax Silica gel column using a mobile phase consisting of 90:10:04 (v/v) mixture of dichloromethane-methanol-aqueous ammonia, 2 ml per min and detection at 249 nm. All NMR spectra were recorded on a 500 MHz Avance III Bruker instrument. N-bromosuccinimide was used without purification all solvents were used as such.

Preparation of diastereomeric palonosetrons (3)

(S)-2-(1-Azabicyclo [2.2.2] oct-3-yl)-2, 4, 5, 6-tetrahydro-1H-benz [de] Isoquinoline-1-one 2 16.5 g along with 20% $Pd(OH)_2$ /C (16.5g, 50.0% wet) in 23.0 volumes of ethyl acetate was stirred at 58.0°C to 62°C under a hydrogen atmosphere (30.0 atmospheres) for approximately 68.0 hours. The catalyst was then filtered and washed with ethyl acetate (20ml) two times. The total ethyl acetate filtrate was then concentrated under vacuum to give 16.5g of the title compound **(3)**

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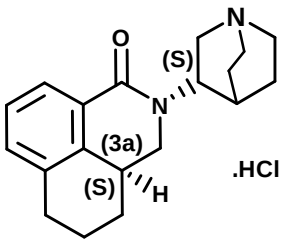
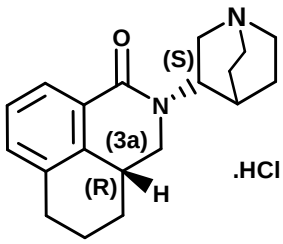


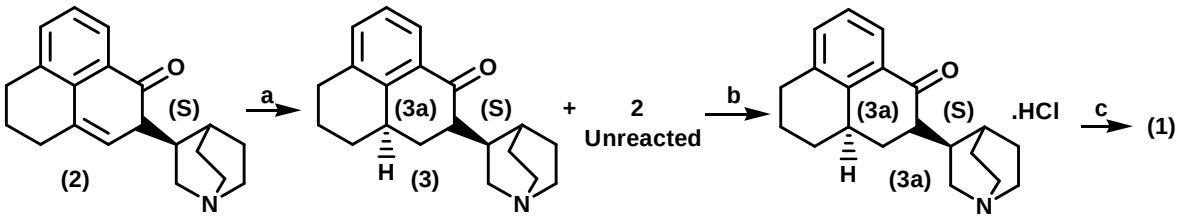
(1)

Figure 2 : Palonosetron hydrochloride



(1a)

Figure 3 : Undesired isomer of palonosetron hydrochloride



Scheme 1 : Reagents and conditions: (a) 20% $Pd(OH)_2/C$, Ethyl acetate, 60°C, 58 hours, H_2 atmosphere (30 psi) (b) HCl (aq.) Methanol/Ethanol, N-bromosuccinimide (cat), 70-75°C, 5.0 min (c) 5% Methanol in Ethanol crystallization

which was found to contain 59.68% of the desired (3aS, S) isomer **(1)**, 39.32% of undesired (3aR, S) isomer **(1a)** and 0.71% of unreacted intermediate **(2)** by HPLC analysis.

Preparation of palonosetron hydrochloride (1)

The diastereomeric palonosetron **(3)** (16.5g) obtained above was dissolved in 5% methanol in ethanol mixture (4.2 volumes). To it hydrochloric acid in ethanol was added and was heated to 70-75°C. Then N-bromosuccinimide (140mg) was added at reflux. The solution was then cooled to 0 to 5°C and 9.0g of the precipitated diastereomeric palonosetron hydrochloride **(3a)** were isolated by filtration. This obtained diastereomeric palonosetron hydrochloride **(3a)** showing 95.90% of the desired (3a S,S) isomer **(1)** and 3.10% of the undesired (3a R,S) isomer **(1a)**, when crystallized twice from ethanol-methanol mixture yielded 5.0g of the title product **(I)** which was found to contain 99.66% of the titled compound **(1)**, 0.29% of (3aR,S) isomer **(1a)** and intermediate **(2)** below detection limit by HPLC analysis.

SOR

94.0° (c = 0.4 in water). IR υ_{max} (KBr) cm^{-1}: 1645, 1591. ^{1}H-NMR (500MHz, CDCl3): δ 1.35-1.47 (m, 1H), 1.68-2.27 (m, 7 H), 2.39-2.42 (m, 1H), 2.74-2.93 (m, 2H), 3.07-3.16 (m, 1H), 3.26-3.38 (m, 4H), 3.58-3.85 (m, 4H), 4.83-4.91(m, 1H), 7.25-7.28 (m, 2H), 7.80-7.85 (m, 1H), 12.19 (S, 1H).

ACKNOWLEDGEMENT

We thank our analytical development section for providing the necessary analytical support.

REFERENCES

[1] Indian Patent Application no 1677/Mum/2009, filed 21 July, 2009; US Patent Application no 12/652,090, Filed 05 January 2010 (Yet to be Published).

[2] EP 0,430,190 and its Equivalent US Patent 5, 202, 333 both belonging to Syntex U.S.A.

[3] Journal of Medicinal Chemistry, **36(18)**, 2645-2657 **(1993)**; US patent 5,510,486 to Syntex U.S.A.; Heterocyles, **43(7) (1996)**; Organic Process & Development, **1**, 117-180 **(1997)**; Synthesis, **8**, 1113-1116 **(2000)**; Pub. No. US 2008/0058367 A1 filed on 28th August, **(2007)**.