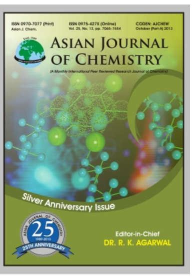
Asian Journal of Chemistry; Vol. 25, No. 18 (2013), 10238-10240

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2013.15244



Synthesis and Characterization of 1-(2-(Dimethylamino)ethyl)-6,6a,7,11-tetrahydro-3*H*,9*H*-oxazolo[3,4-b]pyrrolo[2,3-h]isoquinolin-9-one: A Zolmitriptan Related Impurity

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(*Received*: 31 January 2013; *Accepted*: 11 November 2013) AJC-14374

We report two different synthetic approaches for the synthesis of 1-(2-(dimethylamino)ethyl)-6,6a,7,11-tetrahydro-3*H*,9*H*-oxazolo[3,4-b]-pyrrolo[2,3-h]isoquinolin-9-one (**1**), an important reference standard for the chemical characterization of zolmitriptan. The starting material isoquinolin-3-one (**12**) was obtained with good overall yield starting from commercially available L-phenyl alanine (**7**).

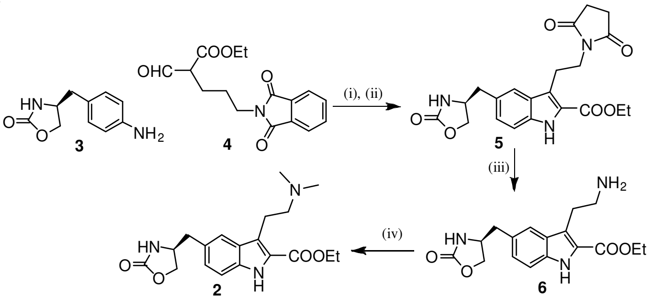
Key Words: Zolmitriptan, L-Phenyl alanine, 1,2,3,4-Tetrahydro isoquinoline-3-carboxylate, 2-Amino-3-(4-nitrophenyl)propanoic acid.

INTRODUCTION

Zolmitriptan[1] is described chemically as (S)-4-({3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl} methyl)-1,3-oxazolidin-2-one (**2**). It is used in the acute treatment of migraine attacks with and without aura and cluster headaches. It is a selective agonist of 5-HT 1B/D receptors. Zolmitriptan is marketed by AstraZeneca with the brand names Zomig, Zomigon (Argentina, Canada & Greece), AscoTop (Germany) and Zomigoro (France). Pharmaceutical impurities consists of reaction by-products generated during the synthesis of active pharmaceutical ingredients (APIs) and degradation products formed during the formulation manufacturing process and the storage of APIs. The presence of these undesired chemicals, also referred to as 'related substances'[2-5] even in small amounts may influence the efficacy and safety of the pharmaceutical products. Indeed, the presence of such impurities and their levels in the drug products are indicative of the product quality and can imply a risk to patient safety.

Impurity profiling (*i.e.*, the identity as well as the quantity of the impurity in the pharmaceuticals) is now receiving important critical attention from regulatory authorities; limits of impurities present in the APIs and formulations are incorporated in pharmacopoeias. Moreover, the International Conference of Harmonization (ICH) has formulated workable guidelines regarding the control of impurities[6]. Although these impurities are usually present at very low levels, it is imperative to characterize their identities in order to make proactive decisions with respect to optimization of synthesis route and formulation development and ultimately to design a control strategy for manufacturing process. For this reason, there is a significant demand for impurity-reference standards along with the API-reference standards for both regulatory authorities and pharmaceutical companies.

The present work is directed towards the development of feasible synthetic routes to prepare 1-(2-(dimethylamino)ethyl)-6,6a,7,11-tetrahydro-3*H*,9*H*-oxazolo[3,4-b]pyrrolo[2,3-h]-isoquinolin-9-one **(Scheme-I)** intended as impurity-reference standard for the chemical characterization of zolmitriptan.



(i) $NaNO_2$, HCl (ii) MeOH, AcONa (iii) aq. HCl, N_2H_4 (iv) HCHO, $NaBH_3CN$, AcOH, Na_2CO_3

Scheme-1: Synthesis of Zolmitriptan intermediate

EXPERIMENTAL

Common reagents and materials were purchased from the sigma Aldrich and solvents were used commercial grade and yields were calculated for compound purified by chromatography.

Thin layer chromatography performed on Merck Kieselgel 60 F_{254} plates eluting with solvents indicated, visualized by 254 nm UV lamp. Nuclear magnetic resonance spectra were acquired at 400 MHz for ^{1}H. Glass ware for all the reactions was oven-dried at 110 ºC and cooled in desiccators.

Methyl 7-nitro-1,2,3,4-tetrahydro isoquinoline-3-carboxylate (8): To a solution of aq. HCl (770 mL) and formalin (230 mL) was added L-phenyl alanine (100 g) at 25-35 ºC. The contents were heated to 90-95 ºC and the reaction mass was stirred for 1 h. The reaction mass was cooled to 60-65 ºC. Aq. HCl (200 mL) followed by formalin (100 mL) were added and heated to 90-95 ºC for 4 h. Cooled the reaction mass to 25-35 ºC, precipitated material filtered and washed with water (100 mL). Wet material was dried at 50-60 ºC. The above compound was added portion wise into mixture of sulphuric acid and nitric acid at -5 to -10 ºC in 1 h and continued stirring for 4 h, after completion of the reaction (vide TLC) quenched into chilled water. pH of the reaction mass was adjusted to 7-8 with ammonia and the contents were stirred for 0.5 h precipitated material filtered and washed with water, wet material dried at 60 ºC. The above compound (70 g) was taken in methanol (490 mL) and cooled to 0-5 ºC. To this solution thionyl chloride (49 mL) was added in 1 h followed by heated to reflux for 4 h. After completion of the reaction (vide TLC) the excess methanol stripped out under vacuum at below 60 ºC to afford methyl 7-nitro-1,2,3,4-tetra hydro isoquinoline-3-carboxylate as a brown coloured solid. m.p. 121-124 ºC; ^{1}H NMR δ = 2.907-2.958 (q, 1H), 3.074-3.118 (dd, 1H), 3.678 (s, 3H), 4.755-3.782 (q, 1H), 3.953-3.986 (q, 1H), 4.039-4.096 (t, 1H), 7.407-7.425 (t, 1H), 7.973-7.981 (d, 1H), 7.981-7.985 (d, 1H); MS: m/e = 237.1 M$^+$.

2-Ethyl 3-methyl 7-nitro-3,4-dihydroisoquinoline-2,3(1*H*)-dicarboxylate (9): Compound-**8** (70 g) was added into mixture of ethyl acetate and water (490 mL), to this sodium carbonate was added at 25-35 ºC and continued stirring for 15 min. To this solution ethylchloroformate was added at 25-35 ºC for 1 h and continued stirring for 2 h. After completion of the reaction (vide TLC) both the layers were separated and compound extracted with ethyl acetate. Total ethyl acetate was distilled under vacuum at below 50 ºC. Reaction mass was cooled to 0-5 ºC followed by thionyl chloride (49 mL) was added in 1h and heated to reflux for 4 h. After completion of the reaction (vide TLC) the excess methanol was distilled under vacuum at below 60 ºC and isolated from IPA to afford **9**. m.p. 120-123 ºC; ^{1}H NMR δ 1.157-1.184 (t, 2H), 1.247-1.276 (t, 2H), 3.296-3.320 (t, 3H), 3.558 (s, 3H) 4.107-4.175 (m, 2H), 4.537-4.632 (q, 1H), 4.742-4.838 (q, 1H), 4.838-5.059 (t, 1H), 7.519-7.535 (d, 1H) 8.049-8.059 (d, 1H), 8.190-8.209 (d 1H); MS: m/e = 309.2 M$^+$.

Ethyl 3-(hydroxymethyl)-7-nitro-3,4-dihydro isoquinoline-2(1*H*)-carboxylate (10): Compound-**9** added into methanol and water mixture followed by cooled to 0-5 ºC. Sodium borohydride was added at 0-5 ºC in 5 equal lots. After addition heated 25-35 ºC and stirred for 2 h. After completion of the reaction (vide TLC) excess sodium borohydride was quenched with acetic acid followed by water was added and extracted with ethyl acetate. Total ethyl acetate was evaporated under vacuum at below 60 ºC to compound **10**. ^{1}H NMR δ 1.124-1.153 (t, 2H), 1.205-1.233 (t, 3H), 3.03 (bs 1H) 3.907-3.949 (q, 1H) 4.078-4.120 (q, 2H), 4.842-4.877 (d, 2H), 6.5 (bs, 1H), 7.452-7.500 (d, 1H), 8.037-8.058 (dd, 1H), 8.144 (bs, 1H); MS: m/e = 280.2 M$^+$.

7-Nitro-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-b]-isoquinolin-3-one (11): Compound **10** added into aq. methanol and caustic flakes followed by reflux for 2 h to form intermediate alcohol[7,8]. Excess methanol was evaporated under reduced pressure. To this reaction mass in methanol lot-2 ethylformate was added was added in 0.5 h and reaction mass was stirred for 2 h. After completion of the reaction (vide TLC) cooled to 25-35 ºC and methanol was saturated with excess water. Extracted with ethyl acetate followed by total solvent was evaporated under vacuum at below 60 ºC to afford 7-nitro-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-b]isoquinolin-3-one (**11**) as brown coloured solid. m.p. 160-162 ºC; ^{1}H NMR δ 2.859-2.914 (q, 1H), 3.116-3.157 (dd, 1H), 4.011-4.056 (m, 1H), 4.155-4.183 (q, 1H), 4.431-4.465(d 1H) 4.541-4.574 (t, 1H), 4.771-4.806 (d, 1H), 7.485-7.502 (d, 1H), 8.044-8.065 (dd, 1H), 8.201-8.205(d, 1H); MS: m/e = 235.2 M$^+$.

7-Amino-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-b]-isoquinolin-3-one (12): Compound-**11** was added into methanol followed by Raney nickel in auto clave. 60 psi hydrogen pressure was applied and reaction mass was stirred for 6-8 h, catalyst was filtered and washed with methanol. Total methanol was distilled under vacuum at below 60 ºC to afford 7-amino-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-b]isoquinolin -3-one **12** as a off-white coloured powder. m.p. 169.2-175.3 ºC; ^{1}H NMR δ 2.542-2.610 (dd, 1H), 2.725-2.773 (dd, 1H), 3.915 (m, 1H), 4.051-4.086 (q, 1H), 4.156-4.198 (d, 1H), 4.421 (s, 1H), 4.463-4.468 (d, 1H), 4.489-4.509 (bs, 1H), 6.356-6.362 (d, 1H), 6.409-6.435 (dd, 1H), 6.807-6.827 (d, 1H); MS: m/e = 205.2 M$^+$.

1-(2-(Dimethylamino)ethyl)-6,6a,7,11-tetrahydro-3*H*,9*H*-oxazolo[3,4-b]pyrrolo[2,3-h]isoquinolin-9-one (1): Compound **12** was added into mixture of water and aq. HCl and cooled to -20- (-10 ºC). for 0.5 h. To this sodium nitride and water mixture was added at -10 ºC and stirred for 2 h. To this solution stannous chloride was added in 20 min at -20 ºC and stirred for 0.5 h followed by heated 25-35 ºC and continued stirred for overnight, after completion of the reaction (vide TLC) pH was adjusted to 1.8-2.0 with caustic lye. Amine compound was added to the above solution 90-95 ºC and continued stirring for 2 h. pH of the reaction mass was adjusted to 6.5-7.0 with NaOH. Undesired material filtered through the hyflow. pH of the filtrate was adjusted to 11-12 and extracted into ethyl acetate and evaporated under vacuum at below 40 ºC, isolated material from isopropyl alcohol and dried the compound at 50-60 ºC to afford **1**. m.p. 193.5-197.4 ºC; ^{1}H NMR δ 2.346 (s, 6H), 2.615-2.645 (t, 2H), 2.979-2.997 (t, 2H) 3.036-3.068 (q, 2H), 4.02 (q, 1H), 4.149-4.175 (t, 1H), 4.84-4.87 (d, 1H), 5.28-5.318 (s, 1H), 6.87-6.89 (d, 1H), 7.037-7.041 (d, 1H), 7.188-7 (d, 1H), 8.290 (s, 1H); MS: m/e = 300.1 M$^+$.

During the laboratory development one unknown impurity (Fig. 1) was observed along with other known impurities and it was characterized and confirmed as below, after isolation from preparative HPLC.

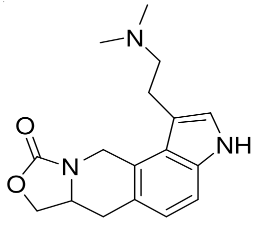


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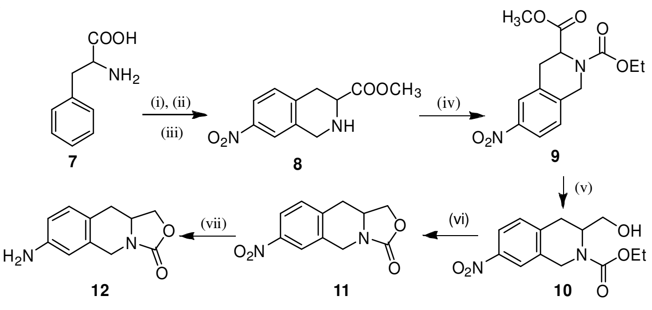
Fig. 1. Structure of impurity

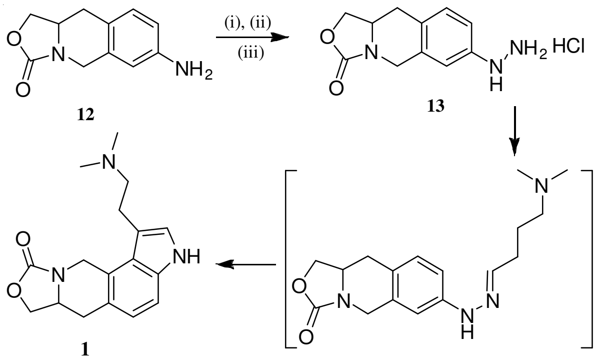
Based on the structure we thought that the impurity is generating during the methylation of **6** with formaldehyde and sodiumcyanoborohydride. In view of this we tried for enrichment by using excess moles of formaldehyde and our attempts were not successful. For analysis and approval of API availability of impurity stock at most important.

The starting compound **8** was synthesised from commercially available compound **7**. L-Phenyl alanine (**7**) was first formylated with formaldehyde and HCl, followed by nitrated with nitrating mixture and finally esterification was carried out with methanol and thionylchloride to get the intermediate **8** which on N-alkylation with ethylchloro formate gave **9**. On reduction with sodium borohydride in methanol, afford **10**. After preparing the alcohol the objective as to take alcohol *in situ* to the intermediate **10** our attempts were made to cyclize **10**, by employing phosgene, afforded **11** with very low yield of 15 %. In order to improve the yield, we switched to optimize the conditions for cyclization of intermediate **10** after decarboxylation, finally we have achieved 75 % yield of **11** by using ethyl formate and sodium methoxide in methanol, intermediate **11** was reduced to get the intermediate **12**. (**Scheme-II**). Which was converted to hydrazine hydride by using sodium nitrite and aqueous hydro-chloric acid afford intermediate **13**. Intermediate **13** was coupled with 4,4-diethoxy-N,N-dimethylbutan-1-amine (**14**) in presence of stannous chloride and HCl afforded 1-(2-(dimethylamino)ethyl)-6,6a,7,11-tetrahydro-3*H*,9*H*-oxazolo[3,4-b]pyrrolo[2,3-h]isoquinolin-9-one (**1**) (**Scheme-III**).



(i) HCHO, aq.HCl (ii) HNO_3, H_2SO_4 (iii) $SOCl_2$, MeOH (iv) ethyl chloroformate, Na_2CO_3 (v) NaOH, $NaBH_4$, MeOH, (vi) ethylchloroformate, CH_3ONa (vii) Raney Ni, H_2

Scheme-II



(i) $NaNO_2$, aq. HCl (ii) $SnCl_2$ (iii) 4,4-dimethoxy-*N*,*N*-dimethylbutan-1-amine (14)

Scheme-III

Conclusion

In summary, the synthesis of 1-(2-(dimethylamino)ethyl)-6,6a,7,11-tetrahydro-3*H*,9*H*-oxazolo[3,4-b]pyrrolo[2,3-h]-isoquinolin-9-one (**1**), which is an important reference standard for the chemical characterization of zolmitriptan with moderate yield is reported.

ACKNOWLEDGEMENTS

The authors thank the Management of R & D, CTO and Dr. Reddy's Laboratories Ltd., for supporting this work. Cooperation from the colleagues from analytical development is highly appreciated.

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