An efficient synthesis of Vildagliptin intermediates

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Received 13 December 2019; accepted (revised) 10 March 2021

Efficient and high yielding methods for the preparation of vildagliptin \textsuperscript{1} intermediate of (S)-1-(2-chloroacetyl) pyrrolidine-2-carbonitrile \textsuperscript{2} and 3-amino-1-adamantane alcohol \textsuperscript{3} respectively have been described. (S)-1-(2-Chloroacetyl) pyrrolidine-2-carbonitrile \textsuperscript{2} has been synthesized from L-proline \textsuperscript{2a} via chloroacetyl chloride, performed with acetonitrile in the presence of sulfuric acid via one-pot reactions. 3-Amino-1-adamantane alcohol \textsuperscript{3} has been prepared from amantadine hydrochloride via oxidation by sulfuric acid/nitric acid and boric acid as catalyst, and has been subjected to ethanol extraction. The overall yield is about 95%.

Keywords: Vildagliptin, intermediate, 3-amino-1-adamantane alcohol, (S)-1-(2-chloroacetyl) pyrrolidine-2-carbonitrile

Diabetes has been one of the three major threats to human health in the 21st century, which is a long-term and chronic metabolic disease that has seriously effect patient’s quality of life. In recent years, the incidence of diabetes has increased rapidly. According to the data, up to 2017, there were about 425 million people suffered from diabetes all over the world. In addition, this number is still on the rise and even up to 629 million in 2040\textsuperscript{1}. Vildagliptin \textsuperscript{1}, designed by Novartis\textsuperscript{2}, is a highly potent, reversible, orally active dipeptidyl peptidase IV (DPP-IV) inhibitor for the treatment of type 2 diabetes. It was announced that vildagliptin \textsuperscript{1} had obtained the European Commission approval to be marketed in 2008, under the trade name of Galvus\textsuperscript{3}. Compared with the traditional oral hypoglycemic agents, vildagliptin \textsuperscript{1} had less side effect\textsuperscript{4}, high drug safety\textsuperscript{5}, almost no side effect causing obesity and other advantages\textsuperscript{6,7}.

With the dramatic increase in the number of diabetics, the demand for vildagliptin \textsuperscript{1} would continue to increase. However, the price of vildagliptin \textsuperscript{1} is so expensive due to the low yield of the important intermediates that ordinary diabetics could not afford it. Therefore, it is a great of significance to improve the synthesis process of vildagliptin intermediates by using cheap raw materials and reagents.

The 3-amino-1-adamantane alcohol \textsuperscript{3} and cyano pyrrolidine moiety \textsuperscript{2} has been found to be an integral part because of the key role in vildagliptin \textsuperscript{1} (Scheme I). In the terms of the relevant literatures, synthetic methods of these intermediates almost have disadvantages of expensive raw materials\textsuperscript{9,10}, complex synthetic routes\textsuperscript{11,12}, as well as low yields\textsuperscript{11}. Therefore it is necessary to develop a simple method with good yield in order to obtain vildagliptin intermediates quickly.

In this context, synthesis of corresponding nitriles from carboxylic acids is not always a simple procedure. We found a facile step one-pot transformation of (S)-1-(2-chloroacetyl) pyrrolidine-2-carboxylic acid \textsuperscript{2b} into nitriles by performing with acetonitrile in the presence of sulfuric acid (Scheme II)\textsuperscript{13}. In addition, we were also synthesis of 3-amino-1-adamantane alcohol \textsuperscript{3}, and was prepared from amantadine hydrochloride via oxidation by sulfuric acid/nitric acid and boric acid (H\textsubscript{3}BO\textsubscript{3}) as catalyst, then the mixture was treated with hydrolysis, acidification. Finally, the mixture was extracted by ethanol extraction technology to get the target compound and the total yield was 95% (Scheme III).

Results and Discussion

In our strategy (Scheme II), we decided to use L-proline \textsuperscript{2a} as raw material on account of its easy
The first step was oxidation. All melting points were.

Unfortunately, several attempts all failed at the end of the conversion of the amide to the corresponding nitrile.

To prepare the ultimate compound - vildagliptin, we also prepared of 3-amino-1-adamantane alcohol 3. Further studies showed that almost all of the researchers select dichloromethane to extract the target product during the preparation of 3-amino-1-adamantane alcohol 3. However, the results of several experiments demonstrated that the efficiency of dichloromethane extraction was considerably low. This was because a bottle-neck of dichloromethane to restrict the improvement of 3-amino-1-adamantane alcohol’s yield. Therefore, it was of great significance and practical application to optimize extraction technology and the conditions of synthesizing of 3-amino-1-adamantanol alcohol 3.

Based on this situation, our group came up with a facile step and high yield synthetic method to synthesize 3-amino-1-adamantane alcohol. As described in Scheme III, the first step was oxidation of amantadine hydrochloride 3a by sulfuric acid/nitric acid (H₂SO₄/HNO₃) and boric acid (H₃BO₃) as catalyst. The second step was hydrolyzation through potassium hydroxide (KOH). The last step was extraction of the target compound by ethanol extraction technology and the total yield was95%.

**Experimental Section**

All reagents and solvents obtained from commercial provenance were of laboratory reagent grade and used as received. All melting points were confirmed by RY-1 capillary melting point meter and are uncorrected. The infrared (IR) spectra were recorded on a spectrophotometer Nicolet FTIR 5700 using the KBr pellet technique. ¹H NMR spectra were gained in CDCl₃ and DMSO-d₆ on Bruker Avance 600 MHz NMR spectrometer. ESI-MS spectra were measured on a Finnigan LCQ Advantage Max spectrometer.

**Synthesis of (S)-1-(2-chloroacetyl) pyrrolidine-2-carboxylic acid, 2b**

To a solution of L-proline (10 g, 0.087 mol) in THF (200 mL), with the slow drop-wise addition of
chboroacetyl chloride (9.8 mL, 0.129 mol) at 0°C and the reaction for 30 minutes. After that, the reaction was stirred for 2 hours at 70°C. After completion of the reaction, diluted with water (25 mL) and stirred for 20 minutes. Then saturated brine (25 mL) and ethyl acetate (150 mL) were added and the organic layer was collected. The aqueous layer was subsequently re-extracted with ethyl acetate (3×50 mL). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$. The filtration was concentrate, which was crystallized by the isopropyl ether to afford compound 2b (14.87g, 89.0%). m.p. 108–110.9°C; IR (KBr): 3425, 3050, 2989, 2940, 2811, 1733, 1625, 1452, 1397 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$): δ 1.97–2.34 (m, 4H, CH$_2$), 3.57–3.74 (m, 2H, CH$_2$), 4.04–4.17 (m, 2H, CH$_2$Cl), 4.55–4.64 (m, 1H, CHCOOH), 12.33–12.47 (s, 1H, COOH); ESI-MS: m/z 192.1 [M+H]$^+$. 

Synthesis of (S)-1-(2-chloroacetyl) pyrrolidine-2-carbonitrile, 2

To a solution of compound 2b (3.0g, 0.016 mol) in MeCN (5 mL) was added slowly Concentrated sulfuric acid (8.5 mL, 0.016 mol) at 95°C and the reaction for 5 hr. Then the excess of acetonitrile was evaporated to give a residue. After that, CH$_2$Cl$_2$ (20 mL) and H$_2$O (15 mL) were added to the mixture, and the organic layer was separated and the aqueous layer was re-extracted with CH$_2$Cl$_2$ (3×30 mL), the combined organic layers were dried over anhydrous Na$_2$SO$_4$. The filtration was concentrated, and was treated with dichloromethane/petroleum ether to give the compound 2 (1.04 g, 38.6%). m.p. 52–54°C; IR (KBr): 3303, 2993, 2986, 2244, 1657, 1421 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$): δ 2.17–2.39 (m, 4H, CH$_2$), 3.57–3.62 (m, 1H, CH$_2$N), 4.06–4.25 (s, 2H, CH$_2$Cl), 4.75–4.86 (m, 1H, CHN); ESI-MS m/z 193.4[M+H]$^+$. 

General procedure for the synthesis of impurity 3-amino-1-adamantane alcohol, 3

Concentrated sulfuric acid (37.5 mL, 98% w/w aqueous solution) was stirred and cooled down to 0–5°C followed by adding nitric acid (3.75 mL, 65% w/w aqueous solution) stirred for 10 minutes, then maintained the temperature of 10-20°C. In the second, the boric acid was added to the mixture and this solution was stirred for 30 minutes, then amantadine hydrochloride (3.75g, 0.020mol) was added to solution in batches until the solid was decentralized completely, the mixture was stirred at 10~20°C for 4 hr. The system was transferred to 3-neck flask (250mL), slowly added crushed ice (60g) into the mixture and stirred for about 30 minutes, until the liquid turned a dark green. After that, the mixture was adjusted to pH>12 by potassium hydroxide, then stirred at 10-20°C for another 4hours to produce large amount of white precipitates and was filtered, then used hydrochloric acid to adjust the pH of filtrate to 7-9. Afterwards, the above reaction solution were concentrated by reduced pressure to afford a white powder, and then anhydrous (80mL) ethanol was added to the powder, then refluxed the mixture for 1 hr. Afterwards, the mixture was naturally cooled down to room temperature and followed by filtration, the clear filtrate was concentrated by reduced pressure to give a white solid, which was treated with acetone/ethyl acetate 10 ml (7:3, v/v). Subsequently, the mixture was warmed to reflux and stirred at 52°C for 1 hr, then filtered the mixture and dried to give the target compound 3 as a white solid (3.20g, 95%). m.p. 262-264°C; IR (KBr): 3364, 3250, 2935, 2839, 1648, 742 cm$^{-1}$; $^1$H NMR (600 MHz, DMSO-d$_6$): δ 1.41-1.56(m, 6H, CH$_2$), 1.65-1.70(d, 6H, CH$_3$), 2.20(s, 2H, CHx2), 4.80(s, 1H, OH), 8.13(br.s, 2H, NH$_3$);$^{13}$C NMR (125 MHz, DMSO-d$_6$): δ 67.7, 52.8, 45.2, 44.6, 44.0, 34.8, 30.7; ESI-MS: m/z 168.2[M+H]$^+$. Anal. Calcd for C$_{10}$H$_{17}$NO: C, 71.85; H, 10.18; N, 8.33. Found: C, 71.82; H, 10.14; N, 8.37%.

Conclusion

In conclusion, we have demonstrated a simple, cost effective route for the synthesis of (S)-1-(2-chloroacetyl) pyrrolidine-2-carbonitrile 2 and a key intermediate for the synthesis of vildagliptin 1. On the other hand, we provided a new method to prepare 3-amino-1-adamantane alcohol 3 which used boric acid (H$_2$BO$_3$) as catalyst and ethanol extraction technology to improve the yield of 3-amino-1-adamantane alcohol. They also bring a practical application value for synthesis of vildagliptin, compared with previously reported methods. Finally, we expect that this process would provide a new idea towards synthesis of vildagliptin 1.

Acknowledgement

The authors are deeply grateful for the support of Chongqing Science and Technology Commission (cstc2019jscx-msxmX0096) for this study. The authors also appreciate the under-graduate innovative experiment program of Chongqing Medical
University (No.201971) for partial financial support of this work.

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