Asian Journal of Chemistry; Vol. 26, No. 18 (2014), 6275-6278

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.17621

An Economical and Facile Method to Synthesize Vildagliptin

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Received: 18 March 2014; *Accepted*: 19 May 2014; *Published online*: 1 September 2014; AJC-15898

A facile and economical synthetic method to prepare vildagliptin with three steps was reported. It was started from L-proline *via* successful reaction with chloroacetyl chloride in tetrahydrofuran to afford 1-(2-chloroacetyl)-pyrrolidine-2-carboxylic acid, followed by reacting with 2-chloro-4,6-dimethoxy-1,3,5-triazine, N-methyl morpholine and 2,4,6-trichloro-1,3,5-triazine to give 1-(2-chloroacetyl)-pyrrolidine-2-carbonitrile which was reacted with 3-aminoadmantanol to get the target compound of vildagliptin.

Keywords: 2-Chloro-4,6-dimethoxy-1,3,5-triazine, 2,4,6-Trichloro-1,3,5-triazine, N-Methyl morpholine, Vildagliptin.

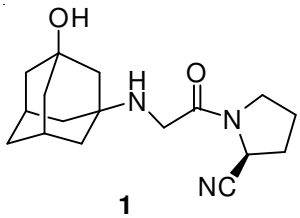
INTRODUCTION

Diabetes mellitus is due to insufficient secretion of insulin[1] or the impaired physiological effects of insulin caused by different causes, resulting in abnormal metabolism of carbohydrate, fat and protein, with main symptoms including chronic hyperglycemia and multisystem chronic lesions. Diabetes mellitus has become the third most wide-spread chronic diseases which threatened human health, following tumor and cardiovascular disease. Its incidence is increasing rapidly, especially in China, Africa and other developing countries.

Diabetes mellitus can be divided into two types, insulin dependent diabetes (type I) and non-insulin dependent diabetes (type II). In addition, type II diabetes mellitus accounts for more than 90 % of the type suffered by patients. Current treatment of type II is mainly pharmacotherapy. A large number of patients with diabetes have promoted the antidiabetic drugs market. Therefore, new effective antidiabetic agents with fewer side effects, such as glucagon-like peptide-1 (GLP-1) analogs and dipeptidyl peptidase IV (DPP-IV) inhibitors, have become the new research focus of global pharmaceutical companies[2].

GLP-1 is an incretin hormone secreted by intestinal L-cells[3], which plays an important role in stimulating insulin release, slowing gastric emptying and inhibiting glucagon release. All of these effects are beneficial to patients with type II diabetes. However, in human bodies GLP-1 will be cleaved within minutes by the enzyme dipeptidyl peptidase IV (DPP-IV)[4], so its half-life is very short. Moreover, the hydrolyzates of GLP-1 not only lose insulin secretagogue activity but also block the GLP-1 receptors. The DPP-IV inhibitors will inhibit the activity of DPP-IV and in turn prolong the half-life of endogenous GLP-1 and thereby indirectly increase insulin secretion, inhibit glucagon secretion, protect the islet β-cells, restore the sensitivity of insulin and slow gastric emptying, which lead to normal blood glucose concentration.

Vildagliptin (**1**) was one of the efficient and competitive DPP-IV inhibitors, which was developed by Novartis and marketed in Europe as the antidiabetic drug in 2007. Its curative effect on type II diabetes is remarkable when used alone or in combination with other drugs. Along with the traditional drugs gradually fading out of the market, it is urgent to research the method with a good yield to prepare vildagliptin with a high purity.



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EXPERIMENTAL

The target compound of vildagliptin synthesized was characterized by ^{1}H NMR, IR, HPLC and LC/MS. The ^{1}H NMR spectra were recorded on a Bruker Avance 400 spectrometer (400 MHz). IR spectra were recorded on a PerkinElmer UK spectrum one with KBr tablet. HPLC purity was determined with an Agilent (model 1200) equipped with a Lichrospher C_{18} column, 250 × 4.6 mm, 5 μm [buffer: 1000 mL 0.1 % phosphate solution of pH 4 with TFA, mobile phase, buffer:

methanol (30:70), 55 min, 214 nm, 1 mL/min]. LC/MS spectra were recorded on an Agilent 6120 single quadrupole LC/MS (model G6120B) equipped with an Agilent C_{18} column, 50 × 2.1 mm, 1.8 μm and a ESI (+) scan mode detector [buffer: 1000 mL water with 1 mL formic acid, mobile phase, buffer: acetonitrile (30:70), 20 min, 210 nm, 0.3 mL/min].

Preparation of 1-(2-chloroacetyl)-pyrrolidine-2-carboxylic acid (3): The L-proline (10 g, 0.087mol) dissolved in 100 mL THF was added to a 250 mL three-neck round bottom flask. Then chloroacetyl chloride (10.5 mL, 0.132 mol) was added dropwise in ice-bath. The reaction mixture was refluxed under stirring for 2.5 h and monitored by TLC (25 % MeOH-CH_2Cl_2). After completing the reaction, the mixture was cooled to about 25 °C, diluted with 20 mL water and stirred for 15 min. Then 20 mL saturated brine and 50 mL ethyl acetate were added and the organic layer was collected. The aqueous layer was re-extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate for 24 h and then concentrated under vacuum. The semisolid residue was stirred in 30 mL diisopropyl ether for 20 min at about 25 °C and then cooled to 0 °C for 24 h to give crystalline white solid which was filtered and washed with cold diisopropyl ether, then dried at 45 °C under vacuum to afford compound **3** (15.8 g, 95 %). m.p. 106-108 °C, IR (KBr, ν_{max}, cm^{-1}): 3420, 3050, 2988, 2941, 2810, 1723, 1610, 1475,1462; ^{1}H NMR (400 MHZ, $CDCl_3$): δ 2.02-2.4 (m, 4H), 3.55-3.8 (m, 2H), 4-4.2 (m, CH_2Cl), 4.65 (m, H, CHCOOH); ^{13}C NMR (75 MHz, DMSO-d_6)[6]: δ 22, 24.5, 28.5, 31.5, 41.6, 41.8, 47.2, 47.6, 59.3, 60, 166.2, 166.5, 174.9, 175.1.

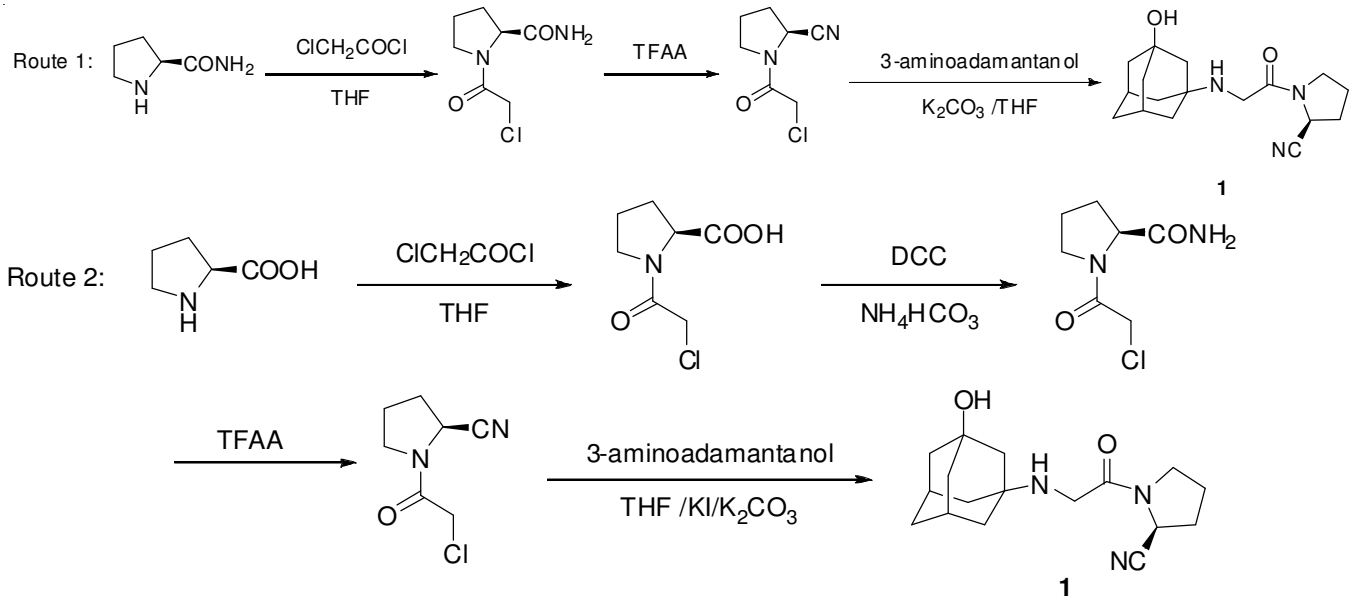
Preparation of 1-(2-chloroacetyl)-pyrrolidine-2-carbonitrile (4): Acetonitrile (50 mL), CDMT (homemade[11,12], 3.85 g, 3.85 mol), NH_4HCO_3 (9.12 g, 0.12 mol) and compound **3** (3.85 g, 0.02 mol) were added to a 150 mL three-neck flask which was equipped with a thermometer, a condenser pipe and a constant pressure funnel. N-Methyl morpholine (2.4 mL, 0.022 mol) was added after the mixture stirred for 10 min. The reaction mixture was stirred at room temperature for 4.5 h and monitored by TLC (95 % CH_2Cl_2-CH_3OH). After completion of the reaction, the mixture was filtered and the filter cake was washed with methylene chloride (3 × 40 mL). The filtrates were collected, combined and concentrated under vacuum to give some oily mass. To this oily mass was added DMF (20 mL) and TCT (2 g, 0.011 mol) and the reaction mixture was then stirred at 40 °C for 4 h. The reaction was monitored by TLC (95 % CH_2Cl_2-CH_3OH). After completing the reaction, water (100 mL) and ethyl acetate (100 mL) were added and the organic layer was collected. The aqueous layer was re-extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with saturated sodium bicarbonate solution (3 × 30 mL) and dried over anhydrous sodium sulfate, then concentrated under vacuum to give a honey-like residue. To this residue 15 mL isopropyl ether was added under stirring, the resulting crystalline solid was filtered and dried at 45 °C under vacuum to afford compound **4** (2.4 g, 70 %). m.p. 62-63 °C, IR (KBr, ν_{max}, cm^{-1}): 2952, 2887, 2241, 1655; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15-2.4 (m, 4H, CH_2), 3.55-3.65 (m, 1H, CH_2), 3.7-3.8 (m, 1H, CH_2), 4.075-4.125 (s, 2H, CH_2Cl), 4.725-4.875 (m, 1H, CHCN); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.5, 24.5, 25, 30, 32.3, 41.7, 46.5, 46.8, 47.1, 117.9, 164.5, 165; MS (*m/z*): 173.1 [M + 1][5].

Preparation of 1-[[(3-hydroxytricyclo[3.3.1.1(3,7)]dec-1-yl)amino]acetyl]-2-pyrrolidine carbonitrile (vildgliptin) (1): 3-Aminoadamantanol (3 g,18 mmol), 2-butanone (21 mL), potassium carbonate (10 g, 72.5 mmol) and potassium iodide (0.25 g, 1.5 mmol) were added to a 150 mL three-neck round bottom flask which was equipped with a condenser pipe, a thermometer and a constant pressure funnel. The mixture was heated to 40 °C under stirring and then the compound **4** (3 g, 16.5 mmol) dissolved in 22 mL THF was added dropwise for 1.5 h. After dropped over, the reaction mixture was stirred at 40 °C for 1 h and then heated up to reflux for 0.5 h. The reaction was monitored by TLC (5 % CH_3OH-CH_2Cl_2). After completing the reaction, the hot mixture was filtered and the filter cake was washed with hot 2-butanone (3 × 20 mL). The collected filtrate was concentrated under vacuum and stirred under slowly cooling. After the mixture became viscous, it was stirred in the ice-bath. The resulting white crystalline solid was filtered and washed with ethyl acetate (3 × 20 mL) and then dried at 45 °C under vacuum to afford the target compound of vildagliptin (4.1 g, 82 %). HPLC purity 99.17 %, m.p. 148-150 °C, IR (KBr, ν_{max}, cm^{-1}): 3293, 2915, 2848, 2241, 1656, 1405; ^{1}H NMR (400 MHz, DMSO-d_6) 1.41-1.49 (m, 14H, CH_2), 1.97-2.02 (m, 2H, OH, NH), 3.44-3.63 (m, 2H, $COCH_2$), 4.70-4.73 (t, 1H, CHCN), 2.10-2.14 (m, 4H, CH_2), 3.26-3.32 (t, 2H, NCH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.07, 34.22, 38.79, 39, 39.21, 39.43, 39.64, 39.85, 40.06, 44.62, 47.09, 47.09, 47.16, 52.72, 68.39, 120.03, 171.32; MS *m/z* 304.2 [M + 1], 305.2 [M + 2][13].

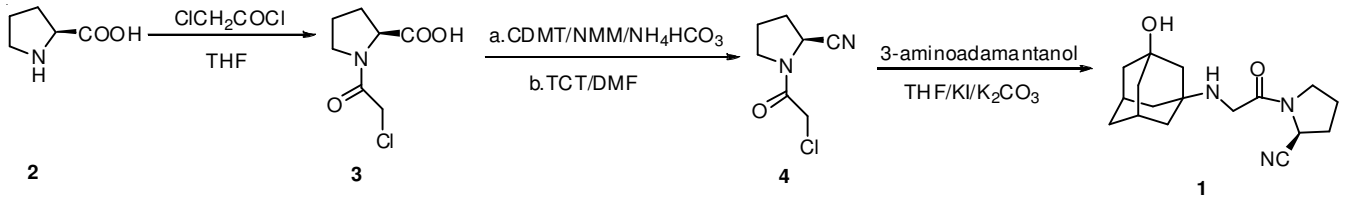
RESULTS AND DISCUSSION

There are several reported approaches to synthesize compound 1shown in **Scheme-I**, but all the methods more or less had some disadvantages. Villhauer *et al*. prepared vildagliptin started from expensive L-prolinamide as shown in route[5] 1. It involved the expensive and corrosive reagent trifluoro acetic acid. Moreover, the purity of the target product could be lowered because the excessive 3-aminoadamantanol was difficult to be removed. Besides, the reaction time was as long as 6 days and the yield was not reported. Singh *et al*.[6] synthesized vildagliptin not only using the expensive trifluoro acetic acid but also the unstable DCC as shown in route 2. Furthermore, the total yield of the target compound was only 18 %. Route 3 was designed by Manne *et al*.[7] to prepare vildagliptin. The use of $(Boc)_2O$ made the reaction process cumbersome and the operation complicated. Moreover, it involved large number of expensive reagents. So it was not suitable for industrial production. Route 4 was the latest reported method to prepare vildagliptin which was researched by our laboratory[8]. This method could afford target compound with relatively good yield and high purity, but it involved four steps and consumed large amounts of reagents, which made the process complex. Therefore, it was not the most efficient way to reduce costs.

In our study, we designed a facile and economical method to afford vildagliptin (**1**) just with three steps (**Scheme-II**) using commercially available and inexpensive raw materials. It was an optimization and improvement of route 4. It was started



Scheme-I: Earlier routes to synthesize vildagliptin



Scheme-II: Synthesis of vildagliptin

from L-proline (**2**) which was N-acylated with chloroacetyl chloride in refluxing THF to afford 1-(2-chloroacetyl)-pyrrolidine-2-carboxylic acid (**3**) as the first step. Chloroacetyl group protected the secondary amino and avoided the procedure of protection and deprotection.

The second step was giving 1-(2-chloroacetyl)-pyrrolidine-2-carbonitrile (**4**). Compound **3** was stirred with CDMT, NMM (N-methyl morpholine) and NH_4HCO_3 in acetonitrile at room temperature. After completion of the reaction, the mixture was filtered and the filtrates were concentrated under vacuum. To the residue were added TCT[9,10] and DMF (dimethyl formamide), then stirred for 4.5 h to afford compound **4**. The intermediate compound **4** was reacted with 3-aminoadamantanol and K_2CO_3 in the refluxing THF to afford the target product of vildagliptin as the last step.

Compared with other routes, our strategy was more suitable for industrial production. We used easily available L-proline instead of the expensive L-prolinamide as the starting material, which could help to cut the reaction costs. Moreover, we utilized compound **3** reacts with CDMT, NMM and TCT in a "one-pot" method to afford compound **4** and did not isolate 1-chloroacetyl-2-pyrrolidine- carboxamide during the entire reaction, which helped to simplify the reaction process and reduce the consumption of the reagents. Besides, the improvement that CDMT was used as ester activator, N-methyl morpholine was used as polyurethane catalyst and TCT was used as dehydrant would made the reaction condition milder, the purification of the product easier and the post-treatment simpler. As a result, all improvements had contributed to increase the yield of vildagliptin.

Conclusion

In conclusion, we have developed a facile and cost-effective method to prepare vildagliptin. This method employed easily available L-proline as starting materials instead of L-prolinamide. Moreover, we synthesized the target product just with three steps, which was beneficial to reducing the reaction time and the costs of vildagliptin.

ACKNOWLEDGEMENTS

This work was supported by Natural Science Foundation of Chongqing (CSTC, 2006BB5286). The authors also thank the Chongqing Medical University for partial financial support to this work.

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