A facile method for the synthesis of 2-(3-hydroxy-1-adamantyl)-2-oxoacetic acid and it's optimization

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Abstract: 2-(3-hydroxy-1-adamantyl)-2-oxoacetic acid (IV), a key intermediate of saxagliptin for type 2 diabetes mellitus (T2DM), was prepared from 1-adamantanecarboxylic acid(I) via oxidation by potassium permanganate(KMnO4) to afford 3-hydroxy-1-adamantanecarboxylic acid (II), which was treated with a one-pot method to give 1-acetyl-3-hydroxyadamantane (III) followed by oxidation. Some key steps were optimized and the overall yield was about 51%.

Keywords: Diabetes, key intermediate, saxagliptin, optimization, one-pot method.

INTRODUCTION

Diabetes is a global disease that seriously threatens the people's health. Up to 2015, there have been 415 millions diabetes patients worldwide, this figure will rise to 642 million by 2040, meanwhile 90% of the total number of diabetes patients were type 2 diabetes patients (IDF Diabetes Atlas, 2015). Saxagliptin (Augeri *et al*., 2005) is a novel anti-diabetic agent, a dipeptidyl peptidase-4 inhibitor co-developed by Bristol-Myers Squibb and AstraZeneca. It was approved for the treatment of the type 2 diabetes mellitus by FDA in 2009 and CFDA in 2011, under the trade name Onglyza® (Yang, 2012). Retrosynthetic analysis of saxagliptin shows that (S)-N-Boc-3-hydroxyadamantylglycine is a key intermediate of Saxagliptin (Savage *et al*., 2009) and (S)-N-Boc-3-hydroxyadamantylglycine was originally prepared from 2-(3-hydroxy-1-adamantyl)-2-oxoacetic acid (IV) by asymmetric reductive amination (Vu *et al*., 2004; Hanson *et al*., 2007) (fig. 1).

According to the reported literatures on the synthesis of 2-(3-hydroxy-1-adamantyl)-2-oxoacetic acid, there are five main methods and they are described in fig. 2. As depicted in Fig. 2, in route one, 1-bromoadamantane react with tris(trimethylsilyloxy)ethylene to provide α-hydroxy-1-adamantane acetic acid, which would required esterification, Swern oxidation, and hydroxylation to afford compound (IV) (Politino *et al*., 2005), this route uses oxalyl chloride and trimethylchlorosilane which are hypertoxic, and the condition of Swern oxidation needs very low temperature (-78°C) which is not good for industrial application. In route two, 1-bromoadamantane react with 1,1-dichloro-2,2-bis(trimethylsilyloxy) ethylene to provide dichloro-1-adamantyl acetic acid methyl ester, which requires hydrolysis and hydroxylation to give (IV), the expensive reagent of this route, especially 1,1-dichloro-2,2-bis(trimethylsilyloxy) ethylene, makes it not suitable for the further study. In route three (Eric and Zachary, 2006), this reaction uses 1-adamantanecarboxylic acid as the starting material which is reacted with dimethyl ketone peroxide to afford 3-hydroxy-1-adamantanecarboxylicacid, which was converted into 1-acety-3-hydroxyladamantane by the presence of CH3Li, then IV was obtained from the oxidation of 1-acety-3-hydroxyladamantane. The reagents in this route are expensive and dangerous, such as dimethyl ketone peroxide and CH3Li, especially CH3Li, it is hardly used to production and quite harmful. Meanwhile, the yield of this route is not high (23%). In route four (Berner *et al*., 2007), IV was obtained through oxidation of 1-acetyl-adamantane in the presence of potassium permanganate, but the yield of this route is not high (36%). Route five is an existing route in our laboratory, in this route, the yield of hydroxylation is quite low, resulting low yield of compound IV, and it wasted too much 2-(1-adamantyl)-2-oxoacetic acid come from a two-step reaction, thereby increased the cost of production (Chen, 2015; Li *et al*., 2012). The respective shortcomings of the five methods above make them difficult for large-scale preparation of compound IV, thereby hindering the large-scale preparation of Saxagliptin.

MATERIALS AND METHODS

Synthesis of 3-hydroxy-1-adamantanecarboxylic acid (II)
To a solution of 1-adamantanecarboxylic acid (10.0g, 0.056mol) in 2% NaOH (100mL) at 55°C was added KMnO4 (10.5g, 0.067mol) during one hour. Then the mixture was stirred at 60°C for 8 hours. Anhydrous sodium sulfite was added followed by filtration. The clear

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filtrate was adjusted to pH2 to produce large amount of white solid, then filtered and dried to afford 3-hydroxy-1-adamantanecarboxylic acid (II) (Yield: 9.25g, 85%). Mp 198-199 °C, ESI -MS (m/z): 219[M + 23]-.

Synthesis of 1-acetyl-3-hydroxyadamantane (III)

A mixture of 3-hydroxy-1-adamantanecarboxylic acid (5 g, 0.026 mol) and SOCl2 (20mL) was stirred and warmed to reflux for 6 hours in the first reactor, and the excess SOCl2 was then distilled off under reduced pressure. The residue was cooled to give 3-chloro-1-adamantane carbonyl-chloride, and then petroleum ether (20mL) was added to the residue for the preparation for the next step. In the second reactor, a solution of diethyl malonate (10mL, 0.057mol) and petroleum ether (20mL) was added dropwise to metallic sodium (1.28g, 0.056mol) in petroleum ether (10mL) at room temperature, and the mixture was then stirred until the metallic sodium was consumed completely. Afterwards, the solution in the first reactor was added slowly to the resulting suspension, and it was then allowed to be stirred at room temperature overnight. Distilled water (80mL) was added to the resulting white suspension, and then the organic layer and water layer were separated. The organic solvent was distilled off under reduced pressure, a mixture of acetic acid (20mL), distilled water (6mL) and concentrated sulfuric acid (2mL) was added to the residue, refluxed for 6 hours. The reaction mixture was allowed to cool to room temperature, and poured into 200mL cold water, extracted with CH2Cl2 (3*10mL), the combined organic phase was washed with brine and removed by reduced pressure, 10% NaOH (50mL) was added to the residue, the mixture was warmed to reflux and stirred for 6 hours. The resulting solution was cooled to room temperature and extracted with CH2Cl2 (3*10mL), the combined organic phase was washed with brine, dried over anhydrous Na2SO4 and the solvent was removed under reduced pressure, the residue was recrystallized from methylene chloride (CH2Cl2)/hexane (1/5) to give colorless orthorhombic crystal, the crystal formed was collected and dried to give 1-acetyl-3-hydroxyadamantane (III) (Yield: 3.7g, 74%). Mp 88-89 °C, 1H NMR (400 MHz, DMSO) δ 4.48 (s, 1H), 2.13 (s, 2H), 2.04 (s, 3H), 1.63– 1.46 (m, 12H); ESI -MS (m/z): 195[M + H]- .

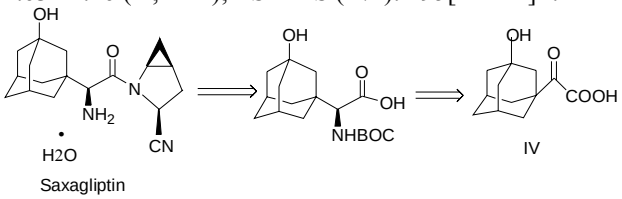

Fig. 1: Retrosynthetic analysis of saxagliptin

Synthesis of 2-(3-hydroxy-1-adamantyl)-2-oxoacetic acid (IV)

To a solution of 3% KOH (100mL) was added a solution of III (5.0g) in tert-butanol (10mL), the contents were heated and controlled at 35°C, then KMnO4 (8.60g) was added portion wise in a period of one hour, afterwards the reaction mixture was stirred at 40°C for another 5 hours. The mixture was quenched with Na2SO3 and then filtered to acquire a clear filtrate, the filtrate was adjusted to pH2 with concentrated HCl and extracted with ethyl acetate (3*10mL) and the combined organic solvent was removed by reduced pressure, the obtained oil was crystallized with ethyl acetate/N-heptane to give 2-(3-hydroxy-1-adamantyl)-2-oxoacetic acid (IV) (Yield: 4.3g, 86%). Mp 162-163°C, 1H NMR (400 MHz, DMSO-d6) δ: 3.32 (br s, 1H), 2.16 (s, 2H), 1.74-1.42 (m 12H); IR (KBr, cm-1) : 3401, 2932, 2861, 2482, 1876, 1713, 1689; ESI-MS(m/z):223[M-H]- .

RESULTS

As depicted in fig. 3, our laboratory improved on previous methods, found a simple and cost-effective method to synthesize IV, it started from 1-adamantanecarboxylic acid. After reacting with KMnO4, the 3-hydroxy-1-adamantanecarboxylic acid (II) which was formed and applied to a one-pot method to yield 1-acetyl-3-hydroxyadamantane (III) and then followed by oxidation to afford IV, the total yield was about 51%.

Compared with the methods mentioned in fig. 2, this route used common and inexpensive reagents, mild reaction conditions, relatively short reaction steps, high yield, especially compared with route five, in the new route, hydroxylation is the first step, this not only increase the yield of hydroxylation, but also reduce the loss of the other intermediate products, ultimately improve the yield of product IV. All these advantages make it suitable for large-scale industrial production. The first step is a common oxidation reaction with a high yield. What has to be mentioned is the second step, it was a novel approach to synthesize 1-acetyl-3-hydroxyadamantane (III), which was obtained through acylation, substitution, decarboxylation and hydroxylation four-step method without any isolating intermediate. The final step was a reaction to oxidate the methyl. Unfortunately, the yield of subsequent direct alkaline oxidation of 1-acetyl-3-hydroxyadamantane (III) with KMnO4 and KOH was a bit low (71%), directly affects the yield of compound IV. The unreasonable usages of KMnO4 and reaction temperatures can not only oxidate the methyl but also oxidate the adamantane ring moiety to generate polyhydroxy compound (main byproduct).

DISCUSSION

Central composite design-response surface methodology can analyze the process parameters of synthesis of compounds, and find the optimal reaction conditions to improve the yield (Feng *et al*., 2013). Therefore we optimized the reaction through central composite design-response surface methodology (Ferreira *et al*., 2007)

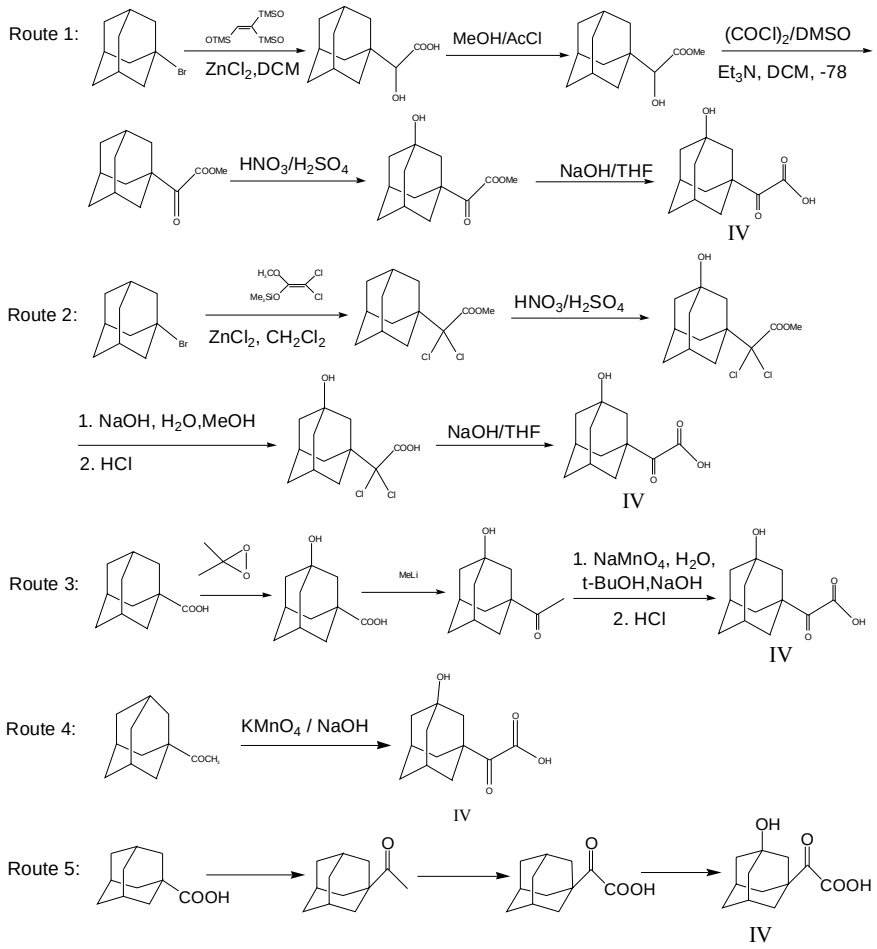

Fig. 2: The existing methods to synthesize IV

Table 1: Level of Factor of product IV in central composite design

Factors/Level	-1.682	-1	0	1	+1.682
X1 (KMnO4,eq)	1.90	1.98	2.10	2.22	2.30
X2 (temperature, ^{o}C)	20	28.11	40	51.89	60
X3 (reaction time, h)	2	3.22	5	6.78	8

focused on three important factors (X1: the equivalent of KMnO4, X2: temperature and X3: reaction time) after factor test study of product IV. The result of single central composite design-response surface methodology was depicted in table 1 and the corresponding response surface of product IV was described in fig. 4. Each factor has been conducted multiple linear regression and binomial fitting by the software of Design-Expert 8.0.6. Multiple linear regression equation was: R (yield) =+84.61-6.02X1 -3.81X2 +0.60X3 (r1=0.188), the binomial equation was: R (yield) =-2551.21+2467.11X1 +1.86X2 +4.96X3 -0.15X1X2 +1.01X1X3 +0.01X2X3 -588.58X12 -0.02X22 -0.69X32 (r2=0.9234). The correlation coefficient of binomial equation r2 was bigger than that of multiple linear regression r1, so the binomial model was ultimately the successful model. fig. 4 which was drew based on the binomial equation shows that, within a certain range, the yield increased as the amount of KMnO4 increased and the temperature rose, as well as when the reaction time increased. Each response surface has its preferable area, and the yield of product could reach maximum in this area. The optimized range of producing IV which was obtained by overlap of each response surface was: X1: 1.98-2.22, X2: 28-52°C, X3: 3-7h. After comprehensive consideration, the finally got optimum process conditions were: KMnO4 (2.1eq), temperature (40°C), reaction time (5 hours), with a good yield of 86%.

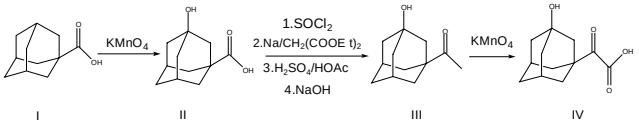

Fig. 3: A convenient approach to prepare IV

General, the impact of various factors on effect is not a linear relationship, people usually use orthogonal design and uniform design to optimize process, but it's less

Table 2: The result of central composite design-response surface methodology of product IV

Number	X1	X2	X3	Actual yield (%)
1	0	0	0	84.92
2	-1	-1	-1	69.32
3	+1	-1	-1	65.86
4	0	0	-1.682	77.99
5	0	0	+1.682	81.46
6	-1.682	0	0	60.66
7	-1	+1	+1	72.79
8	-1	+1	-1	71.06
9	0	0	0	83.19
10	0	0	0	83.19
11	+1	-1	+1	67.59
12	0	+1.682	0	76.26
13	0	-1.682	0	79.72
14	-1	-1	+1	71.06
15	+1	+1	-1	65.86
16	+1	+1	+1	69.32
17	0	0	0	84.92
18	0	0	0	81.46
19	0	0	0	84.92
20	+1.682	0	0	64.12

Table 3: The validation of the optimization result

Condition	Predictive value%	Actual value %	Mean %	Deviation%
KmnO4,2.1eq 40°C 5 h	83.88	84.92	86.22	2.52
		86.66		
		84.92		
		88.39		

predictable, more importantly, it's not sensitive to examine the interaction of various factors. Central composite design-response surface methodology is an experimental method for nonlinear fitting, which can improve the precision and optimize the experimental results. We have developed a simple, low-cost and efficient synthetic approach to IV and 1-acetyl-3-hydroxyadamantane (III) which was synthesized by a one-pot reaction. The compounds of III and IV were all purified by recrystallization which was a simple method for large-scale manufacture.

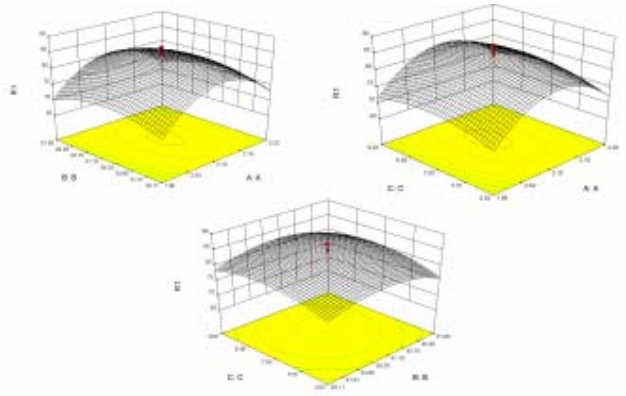

Fig. 4: The response surface of product IV

CONCLUSION

In conclusions, this study introduced a novel method to synthesize 1-acetyl-3-hydroxyadamantane (III), and then to prepare 2-(3-hydroxy-1-adamantyl)-2-oxoacetic acid (IV). It has good repeatability and a relatively high yield. The advantages that avoiding hypertoxic and expensive reagents as well as complex and high demanding reaction conditions make this method suitable for large-scale industry production.

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