# The synthesis of atorvastatin intermediates

Yuanjun Huang[1, a], Ting Liu[2, b]

[1,2]Yichun Vocational Technology College, Yichun, 336000, China

[a]email: nior_0417@sina.com, [b]email: 374486260@QQ.com

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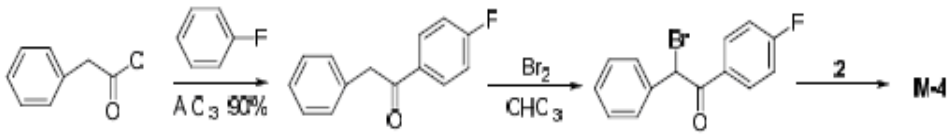
**Abstract:** Adjust the dose of related synthetic method through the experiment, in order to improve the efficiency of the synthesis of intermediates. When adding catalyst 1.8 g, the product yield up to 63.11%; Adding 30g anhydrous ethanol yield up to 61.45%. different materials for the amount of drug income atorvastatin calcium middle size is different, the preparation should be select best dose.

## 1 Introduction

Atorvastatin calcium is one of the clinical use of cholesterol-lowering drugs widely, the main by reducing the generation of HMG-CoA reductase, effectively reduce the body produce cholesterol, low density lipoprotein receptor, causing the body cell synthesis speed, increase and the quantity as well as increase their activity, and promote the low density lipoprotein receptor degradation by, thus reducing the body content of serum low density lipoprotein; It also can effectively reduce the body a decrease in the level of total cholesterol, good antihypertensive effect. Synthesis methods of atorvastatin calcium more variety, of which "- Knorr synthesis, chiral resolution, asymmetric synthesis. The synthesis condition contains reaction temperature, reaction time, and the effect of **catalyst dosage** on the product synthesis ratio. The development of the synthetic methods for two important intermediates provides us new ways and strategies for efficient synthesis atorvastatin calcium [1].




## 2 Experimental Procedures

### 2.1 Experiment instrument and reagent

The laboratory reagent raw material mainly has two ketone (99%), amine ester (99%), toluene, methanol, three methyl acetate (99%), tertiary Ding Jijia ether, n-heptane, THF, sodium hydroxide and hydrochloric acid aqueous solution, anhydrous ethanol, related reagents specifications are analytically pure.

This experiment instrument used mainly for: intelligent constant temperature oil bath pot (suzhou force of instrument technology co., LTD., ST - JDC - HT), the rotary evaporation apparatus (Beijing into cause instrument equipment co., LTD., RE - 5002 type), precision timing electric mixer (jiangsu huanyu scientific instrument factory in jintan city, JJ - type 1), melting point meter (navigation, JH50 type), high performance liquid analyzer (gen analysis instrument co., LTD., hefei countries LC - 20), circulating water type multipurpose vacuum pump (lenk enterprise development co., LTD., Shanghai SHZ - type D).

## 2.2 Synthetic steps

1. Join the Active pharmaceutical ingredients and related reagents in three bottles of apis one after another , three bottles of volume is 500 ml, internal containing water segregator, dry pipe, condenser pipe, mechanical agitator and thermometer, the mixture mixing and heating, then through reflux water, time is about 42.5 h; TLC method for the experiment operation, an agent used for petroleum ether, ethyl acetate (3:1). Raw material drug for: 4 - fluoro - alpha - (2 - methyl - 1 - oxygen generation propyl) - gamma oxygen generation - N, beta diphenyl benzene butyryl 10.8 g, 3 methyl acetate 2.0 g, 6 - aminoethyl - 2, 2 - dimethyl - 1, 3 - dioxane - 4-17.6 g tertiary butyl ketone acetate; Related reagents for: THF41.4 ml, n-heptane, 166.5 ml, toluene 41.4 ml.

2. After waiting for the operation to complete rest for the solution to room temperature, then add 6.9 ml methanol, 124 ml tert-butyl methyl ether, washing solution with sodium hydroxide, and after stratification using hydrochloric acid solution washing organic layer, the isolated layer again, and the organic layer for dry operation, finally can get 30g yellow solid. The yellow solid by anhydrous ethanol 30ml to dissolve, and join the equipped with a condenser pipe and magnetic stirrer stand-up bottle, oil bath heated to 80 ℃, there is about 20 min backflow when starting to cool, stirring overnight after the suction filter, the filter cake using anhydrous ethanol washing, about 10 ml, filtrate and save the merger, the filter cake in vacuum drying under 25 ℃, time of 24 h, the resulting solid white is about 11.3 g is the coarse product. 3, will be made by the crude product with 40 ml ethanol to dissolve, and join the stand-up bottle, heating reflux (80 ℃), month after 20 min can gradually reduce the temperature to 74 ℃, its mixed with activated carbon and silica gel (1:1) of adsorbent was 1.1 g, heat up again to 80 ℃, when in 30 min backflow phenomenon strike filter and down to room temperature, using diatomaceous earth auxiliary filtering, stirring constantly to precipitate crystals, the suction filter after vacuum drying up 9.4 g of solid is obtained by the intermediate.

3. The filtrate obtained by the above operation spinning top up to 20g yellow solid, join to stand-up bottle and add 7ml deionized water and anhydrous ethanol 32 ml, heated 80℃, backflow about 30 min , down to room temperature, Subsequent mixing for the night and the suction filter, also with anhydrous ethanol 10 ml of the filter cake washing, vacuum drying can get 2.6 g of solid, after twice on filter cake refined, can get the target product, 1 g white solid [4-5].

## 3 Results and discussion

### 3.1 The influence of different dosage of catalyst to reaction experiment

In the reaction temperature and reaction time under the condition of invariable, subsequent processing method, fixed amount of other materials besides catalyst, only change (three methyl acetate) the dosage of catalyst, the output of the intermediates, can be observed from the product yield is also different. A total of four experiments, it can be seen when the catalyst is 1.8 g, product yield up to 63.11%. See table 1.

Table 1 The product yield from different catalyst of CRT

| Numble | catalyst dosage（g） | yield（g） | yield of product（%） |
|---|---|---|---|
| 1 | 1.8 | 11.3 | 63.11 |
| 2 | 3.6 | 9.2 | 54.28 |
| 3 | 4.8 | 8.3 | 50.16 |
| 4 | 5.6 | 7.0 | 42.39 |

### 3.2 Different anhydrous ethanol usage influencing on the yield of the product

Holding other conditions unchanged, only in the recrystallization process adding different amount of anhydrous ethanol, observe the product yield, the results available. When add 30 g anhydrous ethanol yield up to 62.55%. See table 2.

Table 2 Different anhydrous ethanol usage influencing on the yield of the product

| Numble | Scheme 1 | Scheme 2 | Scheme 3 |
|---|---|---|---|
| 1 | 60 | 1.3 | 7.29 |
| 2 | 45 | 5.1 | 31.28 |
| 3 | 30 | 11.3 | 62.55 |

## 4 Summary

This experiment with tertiary butyl acetate as raw materials, to produce the intermediate of atorvastatin calcium, through the observation, this paper changes the dosage of the catalyst three methyl acetate and adjustment in the process of using anhydrous ethanol refined its addition amount, eventually the intermediates of yield is different, so in the preparation process to select the optimum addition amount.

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