Synthesis of 1, 2-dihydroazete-3-methyl ester

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Abstract. The invention relate to 1, 2-dihydroazete-3-methyl ester and a series of derivatives, which can be used to treat cardiovascular diseases and hepatitis c virus (HCV). This research mainly describe a synthesis route of the key intermediate for synthetizing Forskolin and HCV NS5B inhibitors. The synthesis routes is mainly consist of three steps of acylation, replacement and hydrolysis. This synthesis route provides some valuable references and experimental basis for the synthesis of Forskolin and HCV NS5B inhibitors.

1. Introduction
Cardiovascular and cerebrovascular diseases are the diseases that seriously endanger human health [1-3]. It is characterized by ischemic or hemorrhagic diseases in heart, brain and systemic tissues caused by hyperlipidemia, blood viscosity, atherosclerosis, and hypertension [4-5]. Middle-aged and elderly people over the age of 50 have high prevalence, high disability and high mortality [6]. Currently, many medicines to treat cardiovascular and cerebrovascular diseases are already developed, among which Forskolin is a typical medicine to treat cardiovascular and cerebrovascular diseases [7]. In this paper, we describerd the synthesis route of 1, 2-dihydroazete-3-methyl ester is an important intermediate for synthesis of Forskolin [8-10]. 1, 2-Dihydroazete-3-methyl ester can also be used to synthesize HCV NS5B inhibitors and treat HCV virus (HCV) [11-14].

Figure 1. Structures of Forskolin  
Figure 2. Structures of HCV ns5B inhibitors

In this study, we synthesized 1, 2-dihydroazete-3-methyl ester. The final product was obtained through acylation, substitution and hydrolysis, making it more suitable for industrial production. Reactions have simple steps, mild conditions, and simple posttreatment prospects. The structure of Forskolin and HCV NS5B inhibitors is shown in figure 1 and figure 2, respectively.
2. Materials and methods
TLC analysis was carried out on silica gel plates GF254 (Qindao Haiyang Chemical, China). Elemental analysis was determined on a Carlo-Erba 1106. Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC–MS (Agilent, Palo Alto, CA, USA). Elemental analysis instrument (Carlo Erba, Milan, Italy). All the materials were obtained from commercial suppliers and used without purification, unless otherwise specified. Yields were not optimized.

3. Synthesis of compounds
The structures and the synthetic route were shown in Scheme 1

4. 3-methyl ester-azetidine (2)
A mixture of acetyl chloride (15.6 g, 0.2 mol) in anhydrous ethanol (CH3OH, 30 ml) was stirred under the condition of ice bath for 75 min. Add azetidine-3-carboxylic acid (10 g, 0.09 mol) to the mixture and stirred overnight at room temperature. The reaction's progress was monitored by TLC. After the reaction was completed, vacuum distillation removed the solvent. The solution was then basified using saturated sodium bicarbonate solution to pH 8. The aqueous solution was extracted with ethyl acetate and combined the organic solution. Vacuum distillation removes solvent and get a yellow oily liquid (13.2 g, 89%). 1H NMR (500 MHz, DMSO-d6) δ 3.69 (s, 3H), 3.35 (dt, J = 10.7, 5.3 Hz, 2H), 3.18 (dt, J = 10.8, 5.3 Hz, 2H), 3.04 (p, J = 5.6 Hz, 1H), 1.73 (p, J = 4.9 Hz, 1H). MS (ESI): m/z 116.1[M+H]+.

5. 3-bromo-3-methyl ester-azetidine (3)
A mixture of 3-methyl ester-azetidine (4 g, 0.02 mol) and azodiisobutyronitrile (AIBN, 0.6 g, 0.004 mol) in THF (50 ml) was stirred under the temperature of 75°C for 70 min. N-Bromosuccinimid e(NBS, 3.56 g, 0.02 mol) was added to the mixture three times, each interval was one hour. The reaction's progress was monitored by TLC. After the reaction was completed, vacuum distillation removed the solvent. The residue was purified by silica gel column (eluant: dichloromethane: methanol =30:1) to obtain a light yellow liquid (3.2 g, 81%). 1H NMR (500 MHz, DMSO-d6) δ 3.69 (s, 3H), 3.35 (dt, J = 10.7, 5.3 Hz, 2H), 3.18 (dt, J = 10.8, 5.3 Hz, 2H), 3.04 (p, J = 5.6 Hz, 1H), 1.73 (p, J = 4.9 Hz, 1H). MS (ESI): m/z 194.2[M+H]+.

6. 1, 2-dihydroazete-3-methyl ester (4)
A mixture of 3-bromo-3-methyl ester-azetidine (1 g, 0.009 mol) and LiOH · H2O (0.4 g, 0.018 mol) in 1, 4 dioxane (30 ml) was stirred at reflux under the temperature of 120°C. The reaction's progress is monitored by TLC. After the reaction was completed, vacuum distillation removed the solvent. The residue was purified by silica gel column (eluant: dichloromethane: methanol =30:1) to obtain a light
yellow liquid (0.9 g, 67%). 1H NMR (500 MHz, DMSO-d6) δ 9.09 (dt, J = 6.6, 5.3 Hz, 1H), 7.88 (d, J = 6.4 Hz, 1H), 4.41 (d, J = 5.3 Hz, 2H), 3.75 (s, 3H). MS (ESI): m/z 114.1[M+H] +.

7. Conclusion
1, 2-Dihydroazete-3-methyl ester was synthesized from commercial 3-carboxycycline through three steps, including esterification, substitution and hydrolysis. The synthesis method and reaction conditions of 1, 2-dihydroazete-3-methyl ester were optimized, and the purity of the product was higher. The reaction had simple steps, mild conditions, simple post-processing and high yield. Therefore, the synthesis method is more suitable for industrial production and has a good application prospect.

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