Study on Synthesis of 6-Pentyl-tetrahydro-thieno [3,4-d]imidazol-2-one

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Keywords: 6-Pentyl-tetrahydro-thieno[3,4-d]imidazol-2-one, Biotin, 5-(2-Oxo-hexahydro-thieno [3,4-d]imidazol-6-yl)-pentanoic acid ,synthesis

Abstract: A synthetic route from 5-(2-Oxo-hexahydro-thieno[3,4-d]imidazol-6-yl)-pentanoic acid (biotin) to 6-Pentyl-tetrahydr o-thieno [3,4-d] imidazol-2-one which have important antibacterial bioactivity was described. The whole route processed in overall 56% yield, including an esterification, a DIBAL-H reduction, a protection and a reduction.

Introduction

Biotin, as shown in Figure 1, also known as the coenzyme R, is a water-soluble vitamin that is important to human beings [1]. Structurally, it is composed of an ureido (tetrahydroimidizalone) ring fused with a tetrahydrothiophene ring and a valeric acid-substituent attached to one of the carbon atoms of the tetrahydrothiophene ring [2]. Biotin is a coenzyme for carboxylaseenzymes, involved in the synthesis of fatty acids, isoleucine, and valine. It is also necessary for the synthesis of vitamin C [3]. Biotin is a kind of nutrients to maintain the body's natural growth and development. Recently, it was reported that biotin could also be helpful in maintaining a steady blood sugar level. In the liver, kidney, yeast and milk there contains the highest concentration of biotin [4].

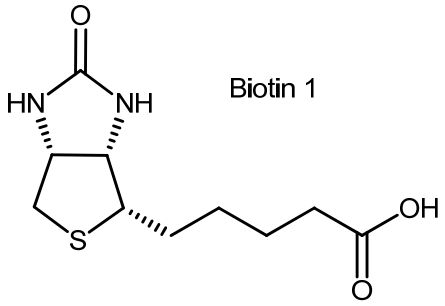
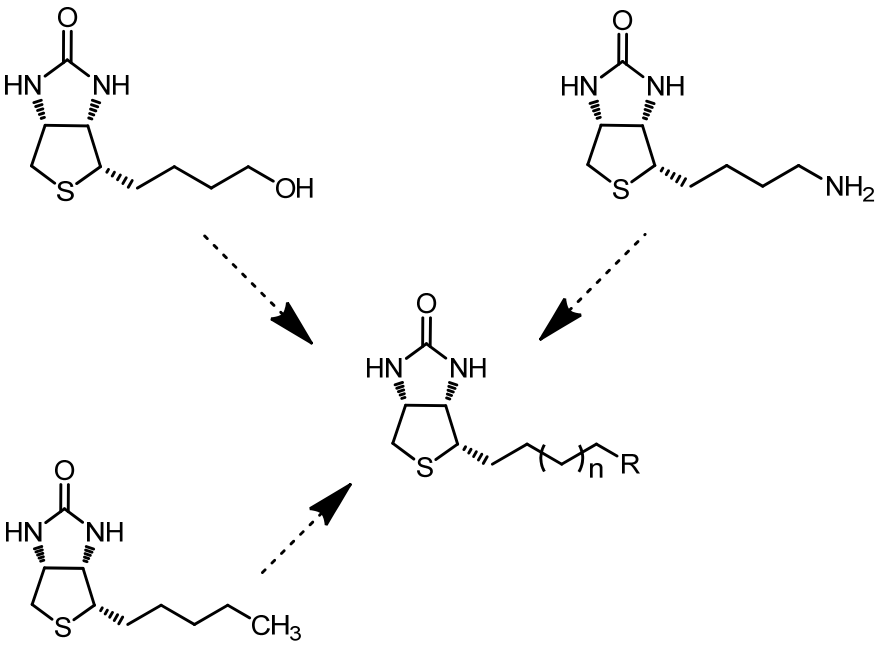


Fig. 1 Biotin 1

Biotin has a series of analogues, and these analogues also possess important bioactivity with very high research value, such as 2-Azidobiotin comprising the ureido ring of natural biotin fusing the thiophene ring. The side chain containing a functional end group, that is the carboxylic acid group, and this side chain was preferably selected to modified to other functional group, such as, amine, alcohol, thiol, aldehyde and a halide and so on [5]. When the carboxylic acid was changed to alkyl group, such as methyl group, it was demonstrated to have antibacterial bioactivity.

Herein, we reported a synthesis of the biotin analogue **2** (showed in figure 2). When R group was replaced by different groups it would gave analogues with different effects. Through inhibiting the clinically important bacteria, comparing with hydroxyl, amino and methyl groups, it was found when the R position is replaced by methyl only needed a small concentration could achieve ideal inhibition mechanism [6]. We became interesting in the SAR of side chain of biotin, as one of the most representative substituted group side chain, so we decided to synthesize such compound via the commercial biotin.

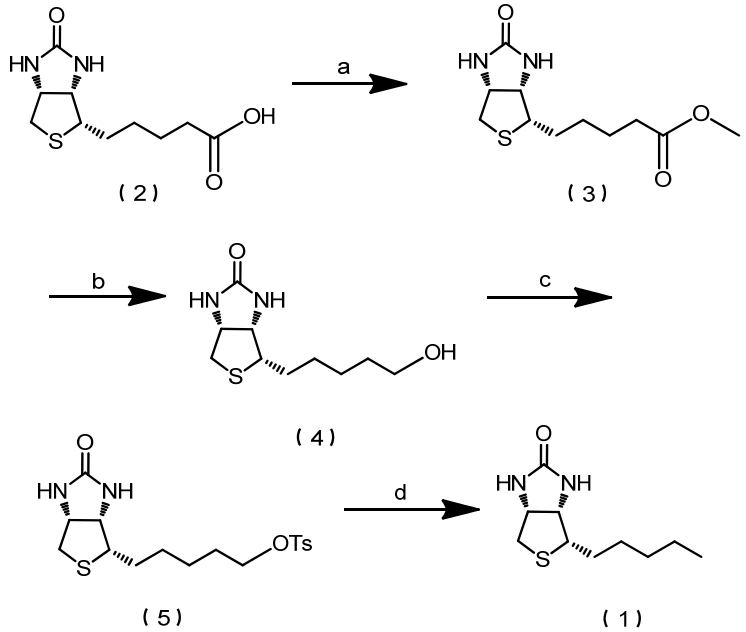


n =1， R =OH、NH_2、CH_3

Fig. 2

Our synthetic route was showed in Figure 3. In our route, we planed to synthesize the target molecule via converting the carboxyl acid group into the methyl group, so it should proceed through an esterification, reduction and removal of the resulting hydroxyl group.

Thus, biotin **2** was transformed into ester **3** in 98% yield upon treatment with acetyl chloride upon in the presence of methanol. Then the ester **3** was reduced by using DIBAL-H at -78℃ in the solvent of dichloromethane to give alcohol **4** in about 100%. Subsequently, the resulting alcohol **4** was treated with TsCl to give compound tosylate **5** which proceeded the reductive removal of with $LiAlH_4$ to gave the desired compoun **1**.



a) acetyl chloride,methanol, 0℃, 98%.
b) DIBAL-H, DCM, -78℃, 2h, 100%.
c) Paratoluensulfony chloride, pyridine, 0℃-25℃, 78%.
d) $LiAlH_4$, THF, reflux, 3h, 56%.

Fig. 3 Synthetic route of Biotin 6-Pentyl-tetrahydro-thieno[3,4-d]imidazol-2-one

Experiment

All reactions were carried out under N_2 atmosphere with dry solvents unless otherwise noted and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (60F-254). Silica gel (200-300 mesh) used for flash column chromatography was supplied by Qingdao Marine chemical factory in China. Anhydrous THF was distilled from sodium-benzophenone. DCM and Et_3N were purified and dried according to standard procedures from CaH_2. Yield refers to chromatographically and spectroscopically (^{1}H NMR), unless otherwise stated. NMR spectra were recorded on either a BRUKER AV-400 MHz (^{1}H: 400 MHz) spectrometer (Nuclear Magnetic Resonance). The chemical shifts are recorded relative to an internal standard of tetramethylsilane standard or relative to chloroform.

5-(2-Oxo-hexahydro-thieno[3,4-d]imidazol-6-yl)-pentanoic acid methyl ester 3

Acetyl chloride (0.55 mL, 6.82 mmol) was added dropwise to 4 mL of methanol in a round bottom flask held at 0℃. After stirring for 15 min, the solution was then added to a room temp suspension of biotin (0.5000 g, 2.05 mmol) in methanol (4 mL) and the reaction was stirred until the biotin was completely consumed (TLC, ~30 min.). Solvent was removed under reduced pressure and the residue was partitioned between sat. $NaHCO_3$ and 5 % methanol in dichloromethane. The separated organic layer was dried over $MgSO_4$ and evaporated under vacuum to obtain compound **3** as a white solid (0.5296 g, 98 percent): ^{1}H NMR ($CDCl_3$, 400 MHz): δ4.59 (dd, *J* = 5.2, 7.7 Hz, 1H), 4.60 (ddd, *J* = 1.8, 4.4, 7.7 Hz, 1H), 3.67 (s, 3H), 3.36 (ddd, *J* = 4.4, 6.1, 8.4 Hz, 1H), 2.97 (dd, *J*= 5.1, 12.4 Hz, 1H), 2.65 (d, *J* = 12.4 Hz, 1H), 2.25 (t, *J* = 7.4 Hz, 3H), 1.68-1.29 (m, 6H).

6-(5-Hydroxy-pentyl)-tetrahydro-thieno[3,4-d]imidazol-2-one 4

Anhydrous DCM (40 mL) was added to biotin methyl ester 3 (0.5296 g, 2.05 mmol) under nitrogen resulting in a colourless suspension. The solution was cooled to -78°C and DIBAL (4.80 mL, 7.12 mmol, 1.5 M in toluene) was added dropwise. After stirring at -78°C for 20 min the solution was allowed to warm to room temperature and was stirred for 2 h. The mixture was again cooled to -78°C and the reaction was quenched by the addition of MeOH (4.5 mL), followed by MeOH:H_2O (15 mL, 2:1). The solvent was removed in vacuo and the residue was purified by column chromatography (DCM:MeOH, 10:1) to give alcohol 4 as a colourless solid (0.1466 g, quantitative). Rf (DCM:MeOH, 9:1) = 0.2; mp 161°C; IR 3415 (OH), 1689 (C=O); ^{1}H NMR δ (400 MHz, $CDCl_3$) 4.59 (1H, dd, *J* = 7.5, 4.6, NHCHCH), 4.60 (1H, dd, *J* = 7.9, 4.5, NHCHCH$_2$), 3.53 (2H, t, *J* = 6.5, CH_2OH), 3.36-2.97 (1H, m, SCH), 2.94 (1H, dd, *J* = 12.8, 5.0, CHAHBS), 2.69 (1H, d, *J* = 12.8, CHAHBS), 1.62-1.48 (4H, m, CH_2), 1.43-1.29 (4H, m, CH_2).

Toluene-4-sulfonicacid-5-(2-oxo-hexahydro-thieno[3,4-d]imidazol-6-yl)-pentyl ester 5

To a stirred solution of biotinol (0.1466g, 0.636 mmol, 1.0 equiv.) in pyridine (3.5 mL) was added tosyl chloride (0.32 g, 1.655 mmol, 2.6 equiv.) at 0°C. After addition, the reaction was allowed to warm to room temperature then stirred for 2 h. The reaction was then submitted to a CH_2Cl_2/1 M H_2SO_4 aqueous solution extraction. The combined organic layers were dried over anhydrous Na_2SO_4, filtered then evaporated under reduced pressure. The residue was rapidly purified by column chromatography on silica gel (EtOAc/MeOH gra-dient) to provide 30 mg of an off-white solid. ^{1}H NMR(400 MHz, $CDCl_3$) δ 4.59 (br s, 1H), 4.60 (br s, 1H), 4.55 (m, 1H), 3.36 (m, 1H), 2.97 (m, 1H), 2.60 (dd, *J* =12.8, 5.2 Hz, 1H), 2.80(t, *J* =7.4 Hz, 2H), 2.74 (d, *J* =12.8 Hz, 1H), 2.35 (s, 3H), 1.64-1.57 (m, 4H), 1.42 (m, 4H).

6-Pentyl-tetrahydro-thieno[3,4-d]imidazol-2-one1

To a solution of biotin tosylate 5 (30 mg, 0.078 mmol) in anhydrous THF (2 mL) was added lithium aluminium hydride (8.65 mg, 0.234 mmol) and the solution was stirred under reflux for 3 h. The reaction mixture was cooled to ambient temperature and were added methanol (1 mL) and saturated aqueous sodium sulphate (2 mL), followed by concentration in vacuo and dissolving with 1:1 dichloromethane and methanol (15 mL) and stirring for 30 min. The solution was filtered and the filtrate was concentrated in vacuo and purified by silica gel chromatography eluting with 3% methanol in dichloromethane to give an off white solid (15.54 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.59 (s, 1H), 4.60 (s, 1H), 3.36 (m, 1H); 2.94 (dd, *J* = 4.8, 12.6 Hz, 1H), 1.62~1.29(d, *J* = 12.6 Hz, 2H), 2.97 (m, 2H), 0.96 (t, *J* = 6.6 Hz, 3H).

Acknowledgement

We gratefully thank the National Natural Science Foundation of China (No.21562020), Science and Technology Research Projects of the Education Department of Jiangxi Province (No. GJJ14579), Science and Technology Plan Project of Jiangxi Province (No. 20142BBE50006), Scientific Research Fund of Jiangxi Provincial Education Department (No. KJLD12036), Training Fund for Excellent young scientist of JiangXi Province (No. [2013]138) for the funding support.

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