Synthesis of *Tert*-butyl 4-formyl-3, 6-dihydropyridine-1(2*H*)-carboxylate

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Abstract: *Tert*-butyl 4-formyl-3, 6-dihydropyridine-1(2*H*)-carboxylate(**9**) is an important intermediate for small molecule anticancer drugs. A rapid and high yield synthetic method for *tert*-butyl 4-formyl-3, 6-dihydropyridine-1(2*H*)-carboxylate was established in this work. The target compound was synthesized from the commercially available piperidin-4-ylmethanol (**5**) through four steps including nucleophilic substitution reaction, oxidation reaction, halogenation reaction and elimination reaction. The structure of the target product was confirmed by ¹H NMR. In addition, the synthetic method was optimized. The total yield of the four steps was high up to 71.4%.

Introduction

Dysfunctional signaling of the PI3K/AKT/mTOR pathway in cancer and its crucial role in cell growth and survival had made it a much desired target for cancer therapeutics [1-4]. The use of tyrosine kinases inhibitors has acquired resistance through secondary mutations or by amplification of genes [5-7]. Although a lot of antitumor drugs have been developed, effective drugs that can overcome this resistance problem have not been discovered so far and have not yet reached clinical trials [8-11]. Therefore we need to continue developing and optimizing anti-tumor inhibitors [12-14]. Indeed, there were many small molecule anticancer drugs had been reported in recent years. Among them, many molecules contained the *tert*-butyl 4-formyl-3, 6-dihydropyridine-1(2*H*)-carboxylate(**9**). The structures of these compounds were shown in Fig.1. For example, 3,5-bis(4-methylbenzoylmethyl)-1-acetyl-4-piperidinone(**1**) [15], methyl 2-(4-benzoyl-1-benzyl-5-ethylpiperidin-3-yl) acetate (**2**) [16], 1-methyl-2-(3-oxo-3-phenylpropyl)-4-phenylpiperidin-4-yl propionate (**3**) [17], 1,3-dibutyl-4-(2-methylbenzoyl)-4,6-diphenyl-3,4-dihydropyridine-2(1*H*)-one (**4**) [18]. Among them, compound **5** can also be used to develop drugs for the treatment of depression and cerebral ischemia, and compound **3** is a potential analgesic.

Fig.1 Intermediates containing the active compound

Therefore, design and synthesis of *tert*-butyl 4-formyl-3, 6 -dihydropyridine -1(2*H*)-carboxylate(**9**) derivative as small molecule inhibitors played a great role in the study of anticancer drugs. In this paper, we have found a fast and high yield synthesized route to *tert*-butyl 4-formyl-3, 6-dihydropyridine-1(2*H*)-carboxylate(**9**). In the step of the whole route, compound **1** rapidly synthesizes target compound **5** through nucleophilic, oxidative, halogenated, eliminated 4-step reactions, make it more suitable for industrial production. Structure of the raw material, intermediate compound of the reaction and target compound was shown in Scheme 1.

Materials and Methods

All melting points were obtained on a Büchi Melting Point B-540 apparatus and were uncorrected. NMR spectra were performed using Bruker 400 MHz spectrometers with TMS 210 as an internal standard. Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC–MS. All the materials were obtained from commercial suppliers and used without purification, unless otherwise specified. Yields were not optimized. TLC analysis was carried out on silica gel plates GF254.

Synthesis of Compounds

The structures and the synthetic route were shown in Scheme 1.

Scheme.1 The synthetic route

Reagents and conditions: (a) (Boc)₂O, THF, r.t.; (b) PCC,DCM, r.t.; (c) NBS,AZBN; (d) LiOH, DMF, heated.

Preparation for *Tert*-butyl 4-(hydroxymethyl) piperidine-1-carboxylate (6)

Compound **5** (20 g, 174 mmol) and (Boc) O₂ (37.9 g, 174 mmol) were dissolved in tetrahydrofuran and stirred at room temperature for 2 hours. The mixture was concentrated and solid was precipitated by adding petroleum ether (500 mL) and suction-filtered to give the target compound **6** (80% yield), ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.86 (m, 2H), 3.42 (m, 4H), 2.04 (m, 2H), 1.49 (s, 9H), 1.40 (m, 3H), 1.16 (s, 1H).

Preparation for *Tert*-butyl 4-formylpiperidine-1-carboxylate (7)

PCC(10 g,46.5 mmol) was added to methylene chloride, N-Boc -piperidine (5 g,23 mmol) alcohol was added to the mixture at once and stirred at room temperature overnight. The mixture was filtered with suction, the filter cake was rinsed with DCM, the filtrates were combined and concentrated to dryness to give the title compound **7**(86% yield)as an oil, ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.72 (s, 1H), 3.88 (m, 2H), 3.41 (m, 2H), 2.60 (s, 1H), 2.35 (m, 2H), 1.75 (m, 2H), 1.49 (s, 9H).

Preparation for *Tert*-butyl 4-bromo-4-formylpiperidine-1-carboxylate (8)

Compound **7**(0.1 g,0.47 mmol) and small amounts of AZBN were dissolved in tetrahydrofuran, warmed to 70 °C, and NBS(0.088 g,0.49 mmol) was added. After two hours of reaction, the mixture was concentrated to give the title compound **8**(86% yield), ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.72 (s, 1H), 3.88 (m, 2H), 3.46 (m, 2H), 2.60 (m, 2H), 2.35 (m, 2H), 1.49 (s, 9H).

Preparation for *Tert*-butyl 4-formyl-3, 6-dihydropyridine-1(2H)-carboxylate (9)

The lithium hydroxide and DMF Stir, then Compound **8**(0.12g, 0.41mmol) was added, the temperature was raised to 70 °C reflux 6 hours. Extracting with water and dichloromethane, dry over anhydrous sodium sulfate and spin the solvent to give the target compound **9**(90% yield), ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.84 (s, 1H), 6.88 (s, 1H), 4.02 (s, 1H), 3.56 (s, 2H), 3.48 (s, 1H), 2.42 (s, 2H), 1.50 (s, 9H).

Conclusions

In conclusion, reactive intermediate compound **5** was synthesized from piperidin-4-ylmethanol through four steps. The purity of the product was much higher than before. Its structure was confirmed by ¹H NMR spectrum.

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