

Synthesis of N-methylthieno [2, 3-d] Pyrimidin-4-amine Thienopyrimidine

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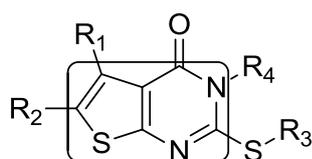
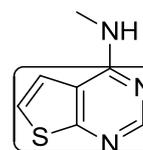
Abstract. Thieno[2,3-*d*]pyrimidine is a key intermediate in many biologically active compounds such as GDC-0941 and BKM 120. In this work, a rapid synthetic method for compound (**4**) was established. The compound (**4**) was synthesized from the commercially available methyl 2-aminothiophene-3-carboxylate and formimidamide through three steps including condensation reaction, chlorination, and nucleophilic substitution. The structure was confirmed by MS and ¹H NMR. Furthermore, the total yield of the three steps was 54%.

Introduction

Cancer is a complex, widespread, and awful disease. That is a group of different diseases character-

Idea by un-controlled cellular growth, tissue damage, and invasion [1]. In 2008, there are 7.6 million people having died of cancer. Nowadays there are many ways deal with cancer; one of the major treatment of cancer is chemotherapy. The anti-tumor drugs not only kill the cancer cells but will also damage the normal cells. Therefore development of a selective inhibition of cancer cell growth of the drug becomes necessary. Many articles reported that cancer is related to the phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathway and normal cells changing. The PI3K pathway is also a common pathway that is activated at abnormally high levels in various human cancers. In recent years, there are many literature had been reported that thienopyrimidine derivatives show a wide variety of biological activities, for example, as an antibacterial and antihypertensive agents, as pesticides, and also as herbicides, even as plant growth regulators[2]. The phosphoinositide 3-kinase (PI3K)/AKT/the mammalian target of rapamycin (mTOR) signal transduction pathway is involved in many essential cellular functions including cell growth, differentiation, proliferation, survival, motility, and intracellular trafficking[3-4]. Thienopyrimidine derivatives were demonstrated to bear nanomolar PI3K α inhibitory potency with over 100-fold selectivity against mTOR kinase[5]. Up to now, there is few literature report that how to synthesis thieno[2,3-*d*]pyrimidine. In order to obtain the target compound, it was synthesized throught three steps, using methyl 2-aminothiophene-3-carboxylate and formamidine acetate as a starting material, including condensation reaction, chlorination and nucleophilic substitution. Most of the synthetic methods of thieno[2,3-*d*]pyrimidine which reported in the literature have the drawbacks such as long synthetic route, harmful to environment and low yield. Therefore, the optimization of the synthetic route and methods of thieno[2,3-*d*]pyrimidine is necessary. At the same times, some literature have reported that the thienopyrimidine core can be used in preparing potent P2Y₁₂ inhibitors[6]. For example, GDC-0941 and BKM 120 are a selective PI3K inhibitors which have been advanced into clinical evaluation[7-10]. At the same times, some literature point out 2-substituted thienopyrimidin-4-one derivatives may serve as novel spasmolytic agents to treat disorders of smooth muscle function, and those compounds have a common features that are thieno [2,3-*d*] pyrimidin[11], the structure of thieno[2,3-*d*]pyrimidin and target compound was shown in Fig. 1.

In this study, we designed and optimized the synthetic methods for *N*-methylthieno[2,3-*d*]pyrimidin-4-amine (**4**) and made it more suitable for industrial production.

Thieno[2,3-*d*]pyrimidin-4-one

Target compound

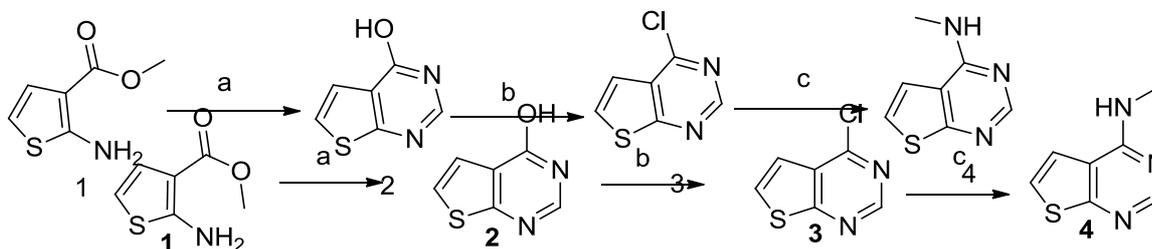
Figure 1. Structure of thieno[2,3-*d*]pyrimidin-4-one and target compound

Materials and Methods

All the chemicals and reagents used in current study were of analytical grade. NMR spectra were performed using Bruker 300 MHz spectrometers (Bruker Bioscience, Billerica, MA, USA) with TMS as an internal standard. Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC–MS (Agilent, Palo Alto, CA, USA). Elemental analysis was determined on a Carlo-Erba 1106 Elemental analysis instrument (Carlo Erba, Milan, Italy). All the materials 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 (Qindao Haiyang Chemical, China).

Synthesis of Compounds

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



Scheme 1. The synthetic route of compound 4

Reagents and Conditions: (a) formamidine acetate, ethanol, 78 °C, 15 h. (b) phosphoryl trichloride, toluene, 110 °C, 1~2 h. (c) 30% methanamine, DMF, 155 °C, 8 h.

Thieno [2,3-*d*] Pyrimidin-4-ol (2). Methyl 2-aminothiophene-3-carboxylate (**1**) (30 g, 190 mmol) and formamidine acetate (25.8 g, 280 mmol) were added in three-necked flask which contain ethanol (50 mL), then stirred and refluxed at 78 °C for 3 h. After the reaction completed, the mixture was poured into ice-cold water. The solid product formed was filtered and crystallized from ethanol. Yield 60%. ¹H NMR (400 MHz, DMSO) δ 12.51 (s, 1H), 8.15 (s, 1H), 7.60 (d, *J* = 0.9 Hz, 1H), 7.42 (dd, *J* = 5.8, 1.4 Hz, 1H). MS (ESI): *m/z* 153.0[M+H]⁺.

4-Chlorothieno [2,3-*d*] Pyrimidine (3). Thieno[2,3-*d*]pyrimidin-4-ol (**2**) (1 g, 6.6 mmol) was suspended in toluene (5 mL), then added the phosphoryl trichloride (10 mL) in the mixture, then at the 110 °C refluxed for 1~2 h. Using the TLC monitoring, after the reaction completed, the mixture was slowly poured into ice-cold water and was stirred at room temperature. The solid product formed was filtered, washed with ice-cold water and dried and crystallized from ethanol. Yield 90%, mp: 97-98 °C. ¹H NMR (400 MHz, DMSO) δ 8.95 (s, 1H), 8.14 (d, *J* = 6.0 Hz, 1H), 7.58 (d, *J* = 6.0 Hz, 1H). MS (ESI): *m/z* 171.9[M+H]⁺.

***N*-methylthieno [2,3-*d*] Pyrimidin-4-Amine.** 4-Chlorothieno [2,3-*d*]pyrimidine (0.46 g, 3 mmol) (**3**) and 30% methanamine (0.2 mL, 30 mmol) were dissolved in *N,N*-dimethylformamide (DMF) at

155 °C for 3 h . After the reaction completed, cooling to room temperature, the target compound was extracted with dichloromethane(DCM) and water from the mixture, dried over anhydrous Na₂SO₄, filtered and evaporated, then to give *N*-methylthieno[2,3-*d*]pyrimidin-4-amine (**4**) in 54% yield, mp: 105-107 °C. ¹H NMR (400 MHz, DMSO) δ 8.35 (s, 1H), 7.99 (s, 1H), 7.55 (s, 1H), 2.97 (s, 3H). MS (ESI): m/z 166.0[M+H]⁺.

Conclusions

In conclusion, *N*-methylthieno[2,3-*d*]pyrimidin-4-amine (**4**) was synthesized from the commercially available methyl 2-aminothiophene-3-carboxylate (**1**) and formamidinium acetate through three steps including condensation reaction, chlorination, nucleophilic substitution. The synthetic method of compound (**4**) and the reactions conditions were optimized, the purity of the product is high. All the compounds structure was confirmed by MS and ¹H NMR spectrum.

Acknowledgments

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