Synthesis of 2-chloro-4-(3-nitrophenoxy) thieno [3, 2-d] pyrimidine

Synthesis of 2-chloro-4-(3-nitrophenoxy) thieno [3, 2-d] pyrimidine

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Abstract. 2, 4-dichloro-6-(3-nitrophenoxy) pyrimidine is an important intermediate of small molecule anticancer drugs. In this work, a rapid synthetic method for target compounds was established. Compound (4) was synthesized from methyl 3-aminothiophene-2-carboxylate and urea through three steps including cyclization, chlorination and nucleophilic substitution. The structure of the target compound was confirmed by ^{1}H NMR and MS spectrum. Furthermore, the synthetic method was optimized. The total yield of the three steps was 42.4%.

1. Introduction

With the development of China's economy and the improvement of people's living standards, great changes have taken place in the diet structure and lifestyle. At the same time, accompanied by the aging of the population and other factors, the incidence and mortality of malignant tumors are rising [1].

2, 4-dichloro-6-(3-nitrophenoxy) pyrimidine (1) is a key intermediate and has a wide range of applications in the pharmaceutical and chemical fields. In recent years, there were many small molecule anticancer drugs had been reported among them many molecules contained the 2, 4-dichloro-6-(3-nitrophenoxy) pyrimidine (1). Therefore, design and synthesis of 2, 4-dichloro-6-(3-nitrophenoxy pyrimidine (1) derivative as small molecule inhibitors played a great role in the study of anticancer drugs. The structures of these co-mpounds were shown in Fig.1. For example, 2-chloro-N-(5-methyl-1H-pyrazol-3-yl)-6-(3-nitrophenoxy)pyrimidin-4-amine (2) [2-3], 1-butyl-5-iodo-4-(3-nitrophenoxy)pyrimidin-2(1H)-one (3**)** [4-5], N-(2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)-5-methyl-4-(3-nitrophenoxy)pyrimidin-2-amine (4) [6-8].

The structures of the intermediate active compounds were shown in Fig. 1

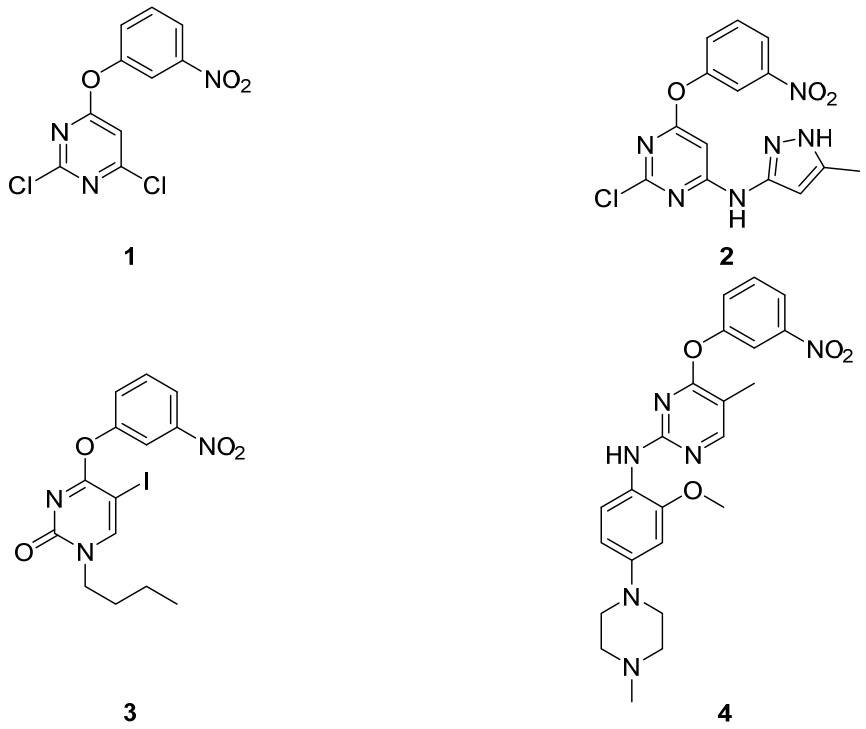


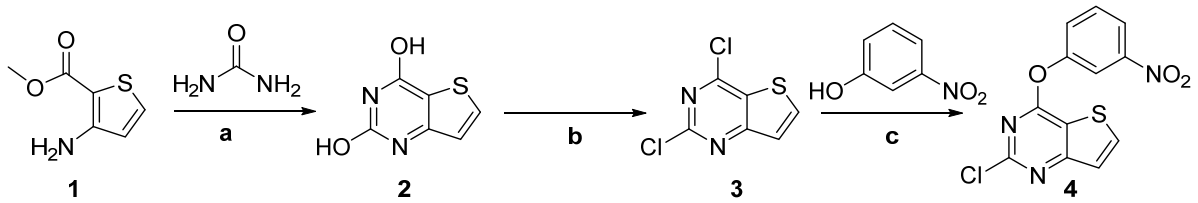
Figure 1. Structures of the intermediate active compounds containing the intermediate

2. Materials and methods

NMR spectra were performed using Bruker 400 MHz spectrometers (Bruker Bioscience, Billerica, MA, USA) with TMS 210 as an internal standard. Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC–MS (Agilent, Palo Alto, CA, USA). 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 (Qindao Haiyang Chemical, China).

3. 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) N_2, 180°C, 4 h; (b) $POCl_3$, DMF, 110°C reflux, 3 h; (c) Cs_2CO_3, 1,4-dioxane, 60°C reflux, 5 h.

4. Preparation for thieno [3, 2-d] pyrimidine-2, 4-diol (2)

To the mixture of 2- amino -4- fluoro benzoic acid (10 g, 64.7 mmol) and urea (30 g, 0.5 mol), in three flasks (250 mL). After stirring for 4h with mechanical agitation at 180°C, the reaction was complete by TLC analysis. Slightly cool down, a saturated aqueous NaHCO3 solution was added, and adding 10% NaOH solution (10 g of NaOH in 100 mL of water). Filtration, the filter cake was transferred to a beaker,

slowly adding the dilute HCl solution and stir the 10 min. Filtration, The filter cake was washed with saturated aqueous NaHCO3 solution, dried to obtain a white solid (7.5 g, 70%).

5. Preparation for 2, 4-dichlorothieno[3,2-d]pyrimidine (3)

A mixture of thieno[3,2-d]pyrimidine-2,4-diol (2) (0.6 g, 3.5 mmol), POCl3 (10 mL) and DMF (3 d) was heated and stirred for 3 h at 120^{o}C, and the reaction was monitored by TLC. The mixture was concentrated under reduced pressure to afford product as viscous oil. Then, the mixture was transferred to a beaker, ice water acetate was added slowly with stirring. Filtration, the filter cake was washed with ice-water, dried to obtain a brown solid (0.53 g, 75.7%). 1H NMR (400 MHz, DMSO-d6) δ 8.68 (d, J = 5.4 Hz, 1H), 7.72 (d, J = 5.4 Hz, 1H).

6. Preparation for 2-chloro-4-(3-nitrophenoxy) thieno [3, 2-d]pyrimidine (4)

A mixture of 2,4-dichlorothieno[3,2-d]pyrimidine (3) (0.5 g, 2.4 mmol), 3-nitrophenol (0.5 g, 3.6 mmol) and Cs_2CO_3 (10 g, 30.6 mmol) was added to flask with 1,4-dioxane (30 mL), heated and stirred for 3 h at 60^{o}C, the reaction was monitored by TLC. The mixture was concentrated under reduced pressure to afford product as viscous oil. DCM was added slowly with stirring. Filtration, dried to obtain an orange solid (0.6 g, 80%). 1H NMR (400 MHz, DMSO-d6) δ 8.51 (d, J = 5.3 Hz, 1H), 8.28 (s, 1H), 8.16 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.74 (t, J = 8.2 Hz, 1H), 7.59 (d, J = 5.4 Hz, 1H).

7. Conclusion

In general, 2-chloro-4-(3-nitrophenoxy) thieno [3, 2-d] pyrimidine (4) was optimized by three steps steps including n cyclization, chlorination and nucleophilic substitution. Due to optimization of the synthesis conditions of the target compound 4, the purity of the product was higher. Its structure was confirmed by 1HNMR spectrum.

Acknowledgments

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