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Synthesis of 8-(2-fluoro-4-nitrophenoxy)-[1, 2, 4] triazolo [4, 3-a] pyrazine

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Abstract. 8-(2-fluoro-4-nitrophenoxy)-[1, 2, 4] triazolo [4, 3-a] pyrazine (1) is an important intermediate in many biologically active compounds. In this work, a rapid synthetic method for compound 1 was established. The compound 1 was synthesized from the commercially available 2, 3-dichloropyrazine (5) through three steps including substitution reaction and ring buckling reaction. The structure was confirmed by MS and ^{1}HNMR. Furthermore, the synthetic method was optimized. The total yield of the three steps was 80.04%.

1. Introduction

Cancer is a serious disease that threatens human health and life. It is caused by the disorder of cell proliferation mechanism [1]. In recent years, the study of signal transduction pathways has become a popular trend in targeted anticancer therapies. Among them, the study on target of receptor tyrosine kinase therapy is an important direction of anticancer drug synthesis and development [2-4]. C-Met is a receptor tyrosine kinase that has been shown to be overexpressed and/or mutated in a variety of malignancies [5]. A number of c-Met activating mutations, many of which are located in the tyrosine kinase domain, have been detected in various solid tumors and have been implicated in invasion and metastasis of tumor cells [6, 7]. Therefore, the development of small molecule inhibitors of c-met is an important field in the research of anti-tumor drugs [8].

In this paper, 8-(2-fluoro-4-nitrophenoxy)-[1, 2, 4] triazolo [4, 3-a] pyrazine (**1**) is a valuable intermediate for the study of small molecule inhibitors of c-met, playing an important role. In recent years, there were many small molecule anticancer drugs had been reported. Among them, many active intermediate compounds are based on [1, 2, 4] triazolo [4, 3-a] pyrazine, which can be linked to many compounds in a variety of ways to enhance the drug's anti-tumor activity [9-12]. The Structures of the intermediate active compounds were shown in Fig. 1. Including 8-(2-fluoro-4-nitrophenoxy)-[1,2,4]triazolo[4,3-a]pyrazine (1) [3], 8-amino-2-(furan-2-yl)-N-(4-hydroxyphenethyl)-[1, 2, 4] triazolo [1, 5-a]pyrazine-6-carboxamide (2) [10], 3-(8-amino-2-(furan-2-yl)-[1, 2, 4] triazolo [1, 5-a]pyrazin-6-yl)phenol (3) [12] and 4-(8-amino-2-(furan-2-yl)-[1,2,4] triazolo[1,5-a]pyrazin-6-yl)-2-methoxyphenol (4) [12]. Among them, 8-(2-fluoro-4-nitrophenoxy)-[1, 2, 4] triazolo [4, 3-a] pyrazine (1) is an important intermediate of novel small molecule c-met anti-tumor compounds. Although its synthesis and design routes have been reported in many literatures in recent years, it has defects of long reaction time and low yield. Therefore, in this paper, we optimized its synthetic route, making the reaction conditions milder, shortening the reaction time, and improving the yield.

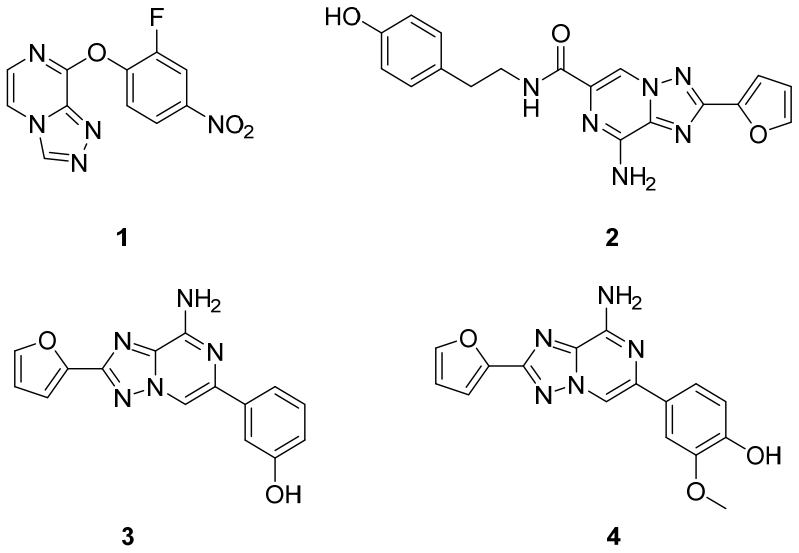


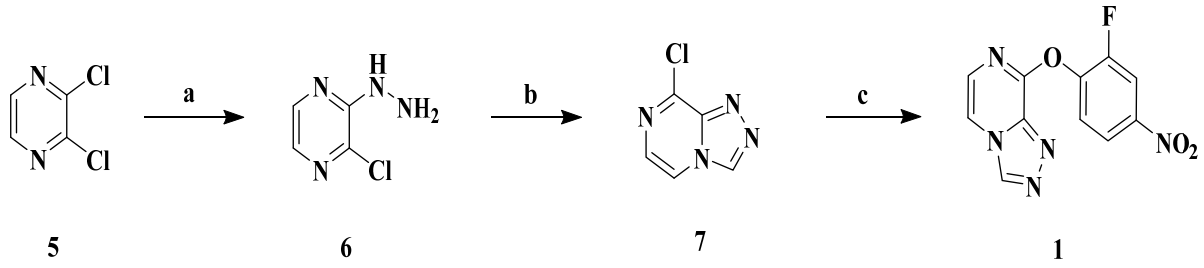
Figure 1. Intermediates containing the active compounds.

2. 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 optimized. TLC analysis was carried out on silica gel plates GF254.

3. Synthesis of Compounds

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



Scheme 1. The synthetic route of compound 1

Reagents and conditions: (a) $N_2H_4 \cdot H_2O$ (80%), ethanol, 85°C, reflux, 2 h; (b) dimethoxymethane, 80°C, reflux, 1.5 h; (c) 1-fluoro-3-nitrobenzene, oxydibenzene, 120°C, reflux, 0.1 h.

4. Preparation of 2-chloro-3-hydrazinylpyrazine

2, 3-dichloropyrazine (**5**) (5.0 g, 0.134 mol) in flask, directly with ethanol (20 mL) as solvent, added a small amount of hydrazine hydrate (5.24 g, 0.42 mol) at a time and added it several times, the reaction is carried out under the 85°C and the reflux device, stirring for 2 h. After cooling, the reaction liquid is added to ice water and stirred and filtered to obtain a yellowish crystal product (6) (4.85 g, 97%). ESI-MS m/z: $[M+H]^+$ 145.02, 1H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.07 (d, J = 2.6 Hz, 1H), 7.57 (d, J = 2.7 Hz, 1H), 4.40 (s, 2H).

5. Preparation of 8-chloro-[1, 2, 4]triazolo[4, 3-a]pyrazine

The 2-chloro-3-hydrazinylpyrazine (6) (5.0 g, 0.035 mol) in flask, with triethyl orthoformate (20 mL) as raw materials and solvents, reaction is carried out under the 80°C and the reflux device, stirring for 1.5 h, reaction after cooling, the suction filter directly, after the suction filter with petroleum ether washing filter cake, get a gray solid product (**7**) (4.62 g, 92.35%). ESI-MS m/z: $[M+H]^+$ 155.01, 1H NMR (400 MHz, DMSO-d_6) δ 9.54 (s, 1H), 7.94 (s, 2H).

6. Preparation of 8-(2-fluoro-4-nitrophenoxy)-[1, 2, 4]triazolo[4,3-a]pyrazine

8-chloro-[1, 2, 4]triazolo[4,3-a]pyrazine (7) (5.0 g, 0.018 mol), and 1-fluoro-3-nitrobenzene (5.7 g, 0.036 mol), in three flask, using oxydibenzene (50 mL) as solvent, reaction under reflux device under 120°C and the reflux device, stirring for 0.1 h, the reaction after completely ethyl acetate is added to the reaction liquid, make the product after fully exhalation, the suction filter, get a yellow solid product (1). (4.47 g, 89.35%). ESI-MS m/z: $[M+H]^+$ 276.04, 1H NMR (400 MHz, DMSO-d_6) δ 9.56 (s, 1H), 8.48 – 8.41 (m, 2H), 8.27 (d, J = 9.5 Hz, 1H), 7.90 (t, J = 8.4 Hz, 1H), 7.42 (d, J = 4.7 Hz, 1H).

7. Conclusion

In general, the synthesis of 8-(2-fluoro-4-nitrophenoxy)-[1, 2, 4] triazolo [4, 3-a] pyrazine (1) from 2, 3-dichloropyrazine was optimized by three steps including substitution reaction and ring buckling reaction. Optimization by synthesis method, the reaction time is shortened, the temperature is relatively mild, the byproduct is less, and the yield of the target compound 1 is higher. Its structure was confirmed by 1H NMR.

Acknowledgments

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