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Synthesis of 4-(pyrrolidin-1-ylmethyl)benzaldehyde

Bin-liang ZHANG[1, a], Lu-jie CAO, Shan XU[1,a] and Ping WANG[1,b,*]

School of Pharmacy, Jiangxi Science & Technology Normal University, Nanchang 330013, China

[a]shanxu9891@126.com , [b]439711557@qq.com

*Corresponding author

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Abstract: 4-(pyrrolidin-1-ylmethyl)benzaldehyde (**1**) as a water-soluble aldehyde is an important intermediate for small molecule anticancer drugs. A rapid and high yield synthetic method for 4-(pyrrolidin-1-ylmethyl)benzaldehyde (**1**) was established in this work. The target compound was synthesized from the commercially available terephthalaldehyde (**6**) through three steps including acetal reaction, nucleophilic reaction and hydrolysis reaction. The structure of the target product was confirmed by ^{1}H NMR and MS. In addition, the synthetic method was optimized. The total yield of the three steps was high up to 68.9%.

Introduction

Cancer is a serious disease that threatens human health and life. More than 100 types of cancer are currently known [1-4]. Most cancers are named after the organ that originally produced the cancer cells, such as rectal cancer, lung cancer and the like[5-6].And also named by the cell type of the cancer cells, for example, cancer cells located on the basal layer of the skin are called basal cell carcinomas carcinoma[7-10]. Cancer is one of biggest killer of human beings, taking the lives of over 7 million people a year. With the further understanding of human signaling pathways, many signaling pathways are found to be closely related to tumors such as EGFR, c-Met and other pathways [11-12]. Through deep research on these pathways, many anti-tumor drugs have been developed, but the drug resistance and adverse side effects are still serious problems [13-14]. Therefore, it is still necessary to continue to develop new antitumor drugs and improve the selectivity, efficiency and safety of anticancer drugs.

In recent years, there were many small molecule anticancer drugs had been reported. Among them, many molecules contained the 4-(pyrrolidin-1-ylmeth yl)benzaldehyde. Therefore, design and synthesis of 4-(pyrrolidin-1-ylmethyl) benzaldehyde derivative as small molecule inhibitors played a great role in the study of anticancer drugs. The structures of these compounds were shown in Fig.1. For example, 4-(((3S,4S)-3, 4-bis(benzyloxy)pyrrolidin-1-yl)methyl)benzaldehyde(**2**)[15], methyl 2-acetyl-4-((2-methyl-5-oxo-3-(p-tolyl)pyrrolidin-1-yl)methyl) benzoate (**3**) [16] , 1-(4-acetyl-2-(4-chloro-3-fluorophenoxy)benzyl)pyrrolidin-2-one(**4**),ethyl 1- (3-acetyl-4- (meth -oxycarbonyl)benzyl)-5-methyl-2-oxo-4-(p-tolyl)pyrrolidine-3-carboxylate(**5**)[17]. At the same time, compound 5 is a potential receptor antagonist with a great potential for research and development, while compound 6 is a potential anti-inflammatory

The synthesis of most 4-(pyrrolidin-1-ylmethyl)benzaldehyde (**1**) is reported. In the literature, there are shortcomings in the synthesis route, such as by-products more, long reaction time. 4-(pyrrolidin-1-ylmethyl)benzaldehyde (**1**) is a key intermediate for anti - breast cancer, lymphoma and colon cancer. Therefore, In this study, we designed and optimized the synthesis of 4-(pyrrolidin-1-ylmethyl)benzaldehydee (**1**),

making it more suitable for industrial production. By optimizing the reaction temperature is less time-consuming, it is important to significantly improve production.

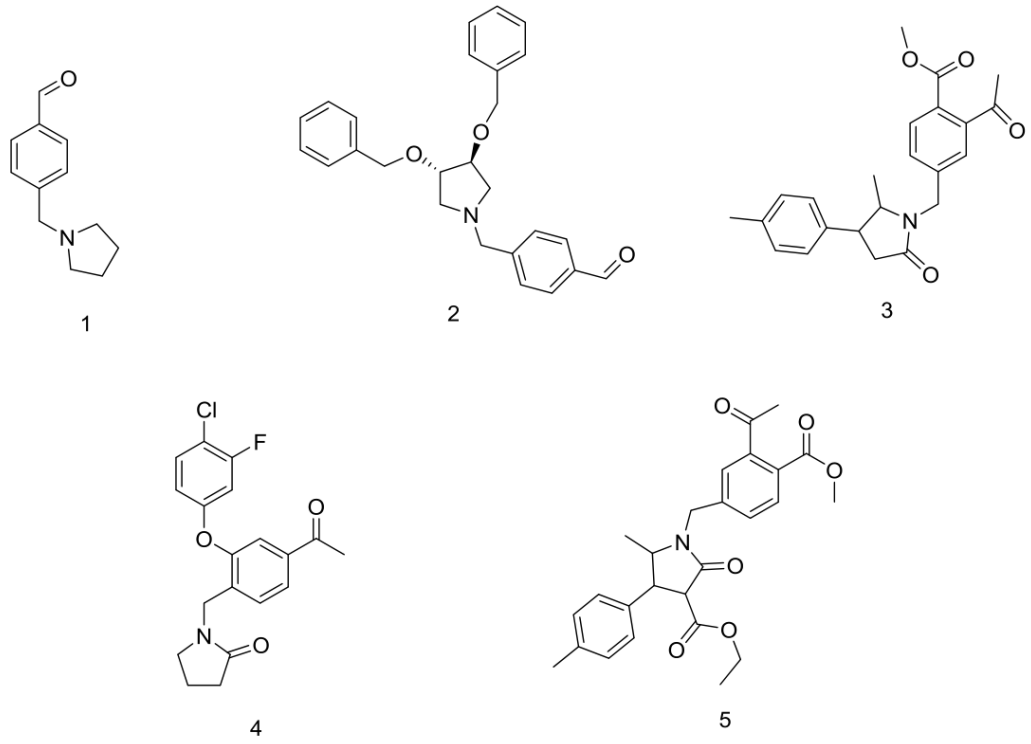


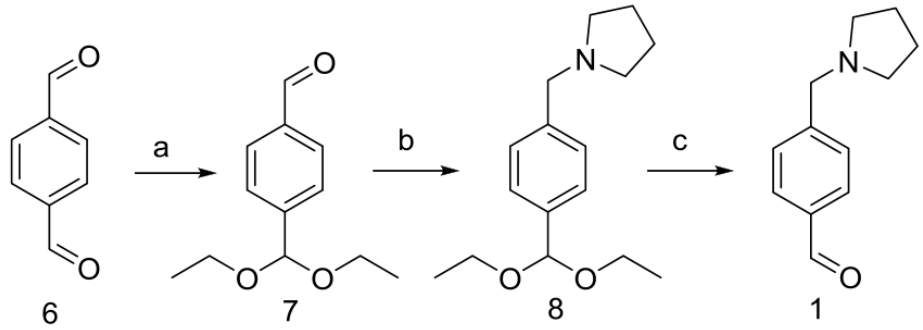
Fig.1 Intermediates and intermediates containing the active compound

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) triethyl orthoformate, ammonium chloride, r.t.; (b) methanol water, sodium borohydride; (c)diluted hydrochloric acid, heated.

Preparation for 4-(diethoxymethyl)benzaldehyde (7)

A mixture of terephthalaldehyde (10 g, 74.55 mmol), ammonium chloride (160 mg, 3.0 mmol) in ethanol (10.3 g, 223.6 mmol) was added triethyl orthoformate (12.15 g, 82 mmol) under ice bath conditions. After the addition, the mixture was stirred at room temperature about 3h. The mixture was concentrated, the residue was purified by silica gel chromatography to give the title compound **7** (yield 60%).

Preparation for 1-(4-(diethoxymethyl)benzyl)pyrrolidine (8)

Compound **7** (8.0 g, 74.55 mmol) was dissolved in methanolic water (methanol: water = 5: 1), stirred well for 2 hours, finally sodium borohydride was added and stirred for 6 hours. The mixture was concentrated, extracted with water and methylene chloride, and the solvent was spin-dried to give the title compound **8** (yield 99%)

Preparation for 4-(pyrrolidin-1-ylmethyl)benzaldehyde (1)

To compound **8** (7.0 g, 36 mmol) in a round bottom flask was added Dilute hydrochloric acid at 80℃. The reaction mixture was magnetically stirred and refluxed for 6 hours until complete by TLC analysis. The reaction mixture was then cooled to room temperature and use sodium carbonate to adjust the pH value to 8 ~ 9. The resulting mixture was diluted extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give the target compound **1**(99% yield).^{1}H NMR (400 MHz, Chloroform-d_6) δ 9.93 (s, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 7.9 Hz, 2H), 4.55 (s, 2H), 3.39 (q, J = 7.0 Hz, 4H), 1.00 (t, J = 7.0 Hz, 6H).

Conclusions

In conclusion, the synthesis of 4-(pyrrolidin-1-ylmethyl)benzaldehyde (**1**) from terephthalaldehyde (**6**) was optimized. Its structure was confirmed by ^{1}H NMR spectrum. The purity of the product was high.

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