Synthesis of Nitrogen-containing 4-alkoxybenzaldehyde Analogues

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Abstract. Nitrogen-containing 4-alkoxybenzaldehyde analogues as a kind of water-soluble aldehyde are important intermediates for small molecule anticancer drugs. A rapid and high yield synthetic method for nitrogen-containing 4-alkoxybenzaldehyde analogues was established in this work. The target compound was synthesized from the commercially available 4-alkoxybenzaldehyde through two steps nucleophilic substitution. The structure of the target product was confirmed by 1HNMR and MS. In addition, the synthetic method was optimized. The total yield of the two steps was high up to 99%.

Introduction

Growth factors and their transmembrane receptor tyrosine kinases play vital roles in cell proliferation, survival, migration and differentiation. The epidermal growth factor receptor (EGFR), a growth-factor-receptor tyrosine kinase, appears to promote solid tumour growth, and its cognate ligands have been identified as a common component of multiple cancer types [1, 2]. Therefore, a number of studies have been reported on EGFR inhibitors. Indeed, many compounds that inhibit EGFR pathway have been found and clinically used for several years such as Gefitinib, Afatinib, Dacamitinib and Canertinib [3] (Fig. 1). Afatinib is an irreversible ErbB-family blocker with preclinical activity in non-small-cell lung cancer (NSCLC) with EGFR mutations. It has been reported that Afatinib is suitable for advanced non-small cell lung cancer (NSCLC) and HER2-positive patients, and shows great effect [4]. However, the use of tyrosine kinase inhibitors has acquired resistance through secondary mutations or by amplification of genes. Up to now, EGFR inhibitors that can overcome this resistance problem have not been discovered or have not yet reached clinical trials [3]. Therefore it is a hotspot to find out superior compounds. Indeed, our research group had spent much time synthesizing Afatinib derivatives to find compounds that show more potency. During the development process of these kinds of new compounds, nitrogen-containing 4-alkoxybenzaldehyde analogues play an important role since they have wide usefulness in the pharmaceutical and chemical fields [5-7]. These groups are frequently focused of interest in medicinal chemistry because of their broad spectrum of activities: anticancer, antimicrobial, antiviral, analgesic, anti-inflammatory, antimicrobial, antihistaminic, antiangiogenic etc. Some of the structures of the nitrogen-containing 4-alkoxybenzaldehyde analogues found in literatures are shown in Fig. 2.
Many researchers have studied the synthesis ways, organic application and pharmacological effects about nitrogen-containing 4-alkoxybenzaldehyde analogues [7-10]. In this paper, we have found a fast and high yield synthesized route to obtain them with 4-hydroxybenzaldehyde being the raw materials. After two steps of nucleophilic substitution, 4-alkoxybenzaldehyde analogues were obtained with a yield of 99%, which makes it more suitable for industrial production. The synthesis route is shown in Scheme.1.

Materials and Methods

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 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).
Synthesis of Compounds

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

**Scheme 1 The synthetic route**

Reagents and conditions: (a) 1-chloro-2-bromoethane, acetonitriles, anhydrous K$_2$CO$_3$, 1h, rt; (b) DMF, microwave, Dimethyl amine, 1h, rt.

**Preparation for 4- (2-chloroalkoxy) Benzaldehyde (2a-b)**

4-hydroxybenzaldehyde (10 mmol) and anhydrous K$_2$CO$_3$ (15 mmol) were dissolved in acetonitriles about 10 milliliter. Then 1-chloro-2-bromoethane (10 mmol) (or 1-chloro-2-methyl bromide) was added into the mixture. And the mixture was refluxed at 82 °C in an oil bath. 6 hours later, put the mixture cool to room temperature. The reaction was stopped by adding suitable water and Ethyl acetate of twice the amount. The combined organic layer was dried over anhydrous Na$_2$SO$_4$. Concentrate organic layer under vacuum to afford crude product to yield a brown liquid. The residue was purified by silica gel chromatography.

4-(2-chloroethoxy)benzaldehyde: $^1$H NMR (400 MHz, CDCl$_3$) δ 9.86 (s, 1H), 7.87 (t, $J$ = 12.8 Hz, 2H), 7.12 (d, $J$ = 7.9 Hz, 2H), 4.17 (dd, $J$ = 14.5, 8.9 Hz, 2H), 3.78 (t, $J$ = 6.1 Hz, 2H). MS (ESI): m/z [M+H] + 184.

**Preparation for 4- alkoxybenzaldehyde (3a-g)**

2a-b (10 mmol) and dimethyl amine (15 mmol) were dissolved in DMF (7ml). Target compound was obtained by using Microwave machine under the condition of 105 °C, 100w, 150PSI. After 1 hour, we finally yield a brown liquid.

4-(2-(diethylamino)ethoxy)benzaldehyde: $^1$H NMR (400 MHz, CDCl$_3$) δ 9.21 (s, 1H), 7.21 (d, $J$ = 8.4 Hz, 2H), 6.48 (d, $J$ = 8.4 Hz, 2H), 3.51 (t, $J$ = 5.6 Hz, 2H), 1.99 (t, $J$ = 5.5 Hz, 2H), 1.56 (s, 6H). MS (ESI): m/z [M+H] + 221.

**Conclusion**

In conclusion, four 4-alkoxybenzaldehyde analogues were synthesized from the commercially available 4-hydroxybenzaldehyde through two steps of nucleophilic substitution reactions. Its structure was confirmed by $^1$H NMR spectrum. The purity of the product was high.

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