Synthesis of 1-(N, N-dimethyl) amine-2-(o-chlorobenzoyl)-methyl acrylate

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Abstract. 1-(N, N-dimethyl) amine-2-(o-chlorobenzoyl)-methyl acrylate is an important intermediate for the many biologically active anticancer drugs. In this research, a rapid and efficient synthesis of compounds 8 was established. Compound 8 consisting of o-chloroacetophenone and dimethyl carbonate was synthesized by two steps including nucleophilic substitution and carbanion reaction. The synthesis method was optimized, and structure was confirmed by 1H NMR and MS spectrum. The synthesis method is optimized. The total yield of the two steps is 63.69%.

1. Introduction
Primary liver cancer is one of the most common and malignant tumors in the world, among of them is hepatocellular carcinoma (HCC), and others are intrahepatic cholangiocarcinoma (ICC). According to some research, the incidence of liver cancer in China ranked fourth in all cancers in 2015, however, the mortality rate ranked third [1]. In recent years, cancer cure methods are constantly being explored. Cancer treatment strategies include physical therapy and chemotherapy, however molecular targeted therapy is currently the most promising treatment for anti-tumor. Some scholars have conducted research on the molecular targeting inhibitor c-Met. At the molecular level, tumors treatment strategy haven gradually entered the era of new targeted therapy. It has been found that hepatocyte growth factor (HGF) and its receptor c-Met play an important role in tumor growth, invasion and angiogenesis as well as c-Met become an important target for anti-tumor therapy. [2, 3] The c-Met signaling pathway is involved in the development of tumors, and its abnormal expression is found in a variety of malignant tumor tissues, which is closely related to tumor prognosis [4, 5]. Tendency anti-tumor research is mainly focused on the development of c-Met inhibitors.

Recently, some research have reported on small molecules against cancer containing methyl (Z)-2-(2-chlorobenzoyl)-3-(dimethylamino) acrylate. Moreover, the design and synthesis of this compound derivative as a small molecule inhibitor has been played in the anticancer drugs. The structures of these compounds as shown Fig.1, N-(2,4-difluorobenzyl)-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamide [6], 4-chloro-N-(4-(2,3-dimethoxy-2,3-dihydropyridin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1, 2-dihydroquinoline-3-carboxamide [7], methyl(Z)-2-(3-(3-chloro-2-fluorobenzyl)-2, 6-difluorobenzoyl)-3-(ethylamino)acrylate [8], 4-hydroxy-2-oxo-1-phenyl-N-(pyrrolidin-1-yl)-1, 2-dihydro-1,8-naphthyridine-3-carboxamide [9], N-benzyl-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamide [10], 1-dicarboxamideMostsyntheticmethodsformethyl(Z)-2-(2-chlorobenzoyl)-3-(dimethylamino)acrylate have been reported, and there are defects in the
synthetic route in the literature, including substitution reactions and aldol condensation reactions. While the product and reaction temperature was high and by-products was harmful to the environment.

In addition, methyl (Z)-2-(2-chlorobenzoyl)-3-(dimethylamino) acrylate is an important intermediate for many tumors inhibitor such as breast cancer and Lung cancer. During the experiment, 1-(N, N-dimethyl) amine-2-(o-chlorobenzoyl)-methyl acrylate was optimized and designed to be more in line with industrial production. The operation not takes less time but the effect is more obvious, moreover, the quality is better and the temperature is controlled.

Figure 1. Active compound containing an intermediate

2. Materials and methods
NMR spectra were performed using Bruker 400 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). 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 compounds 8

Reagents and conditions: (a) o-chloroacetophenone, toluene, NaH, dimethyl carbonate, 120°C; (b) DMA-DMF, 120°C.
4. Methyl 1-(2-chlorophenyl)-acetoacetate (7)
O-chloroacetophenone 3 g in toluene (8-10 mL), slowly add NaH (2.8 g, 0.12 mol) at ice bath, stir for 30 min, add dimethyl carbonate (5.2 g, 0.06 mol), at 120°C, the reaction was judged by TLC, for 2 hours to observe the reaction completely. Post-treatment: The reaction solution was cooled to room temperature, adjusted to pH = 6 with glacial acetic acid, adding 15 mL water, extracted with dichloromethane, and concentrated, and the next step. The yield was 4.1 g and the actual yield was 81%, which was 3.32 g.

5. 1-(N, N-dimethyl)amine-2-(o-chlorobenzoyl)-methyl acrylate (8)
The product Methyl 1-(2-chlorophenyl)-acetoacetate obtained in the previous step is directly added to an appropriate amount of toluene (5-6 mL), and a certain proportion of DMA-DMF is added (b₁ is added to 8.5 mL of b₂, 6.8 mL is actually added to 4 mL), and the reaction time is 2 h at 120°C. Post-treatment: The reaction was completed, and an appropriate amount of saturated brine (yield of DMA-DMF) was added, extracted with dichloromethane, and concentrated to give a yellow oily liquid. The theoretical value of is 4.7 g, the yield is 81%, and the actual value is 3.807 g.

6. 1-(N, N-dimethyl)amine-2-(o-chlorobenzoyl)-methyl acrylate (8)
Brown solid. The yield was 65.6%. 1H NMR (400 MHz, DMSO-d₆) δ 7.61 (s, 1H), 7.49 (s, 1H), 7.33 (d, J = 7.0 Hz, 1H), 7.27 (d, J = 5.6 Hz, 1H), 7.20 (s, 1H), 3.22 (s, 3H), 2.76 (s, 6H); ESI-MS m/z: [M+H]+ 267.5.

7. Conclusion
Typically, o-chloroacetophenone and Dimethyl carbonate are synthesized by two steps including nucleophilic substitution and carbon anion reaction. The optimization of the synthesis method is instrumental for shorting reaction time, maintaining mild temperature as well as the small by-products and then the yield of the target compound 8 is high. Its structure was confirmed by 1H NMR.

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