

Communication

Efficient and Eco-Friendly Preparation of 4-Methyl-5-formyl-thiazole

Nan Bai, Yaowu Sha* and Ge Meng

The Key Laboratory of Bioorganic Phosphorous Chemistry and Chemical Biology, Department of Chemistry, Tsinghua University, Beijing 100084, P.R. China

* Author to whom correspondence should be addressed; E-mail: shayw@tsinghua.edu.cn

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Abstract: 4-Methyl-5-formylthiazole, an intermediate for synthesizing cefditoren pivoxil, was prepared in good yield by Pd/BaSO₄ catalyzed hydrogenation of 4-methylthiazole-5-carboxylic acid chloride. Detailed reaction conditions have been studied.

Keywords: 4-Methyl-5-formylthiazole, Pd/BaSO₄ catalyzed hydrogenation.

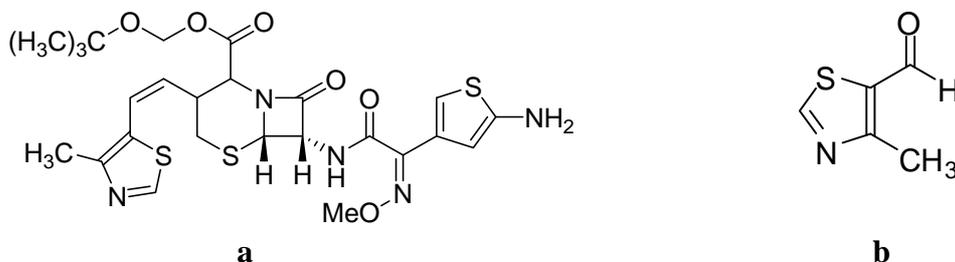
Introduction

Cefditoren pivoxil (**a**, Figure 1) is a third-generation cephalosporin antibacterial with broad-spectrum and enhanced stability against many common β -lactamases. It has been approved in many countries for the treatment of adults and adolescents with acute exacerbations of chronic bronchitis (AECB), community-acquired pneumonia (CAP), streptococcal pharyngitis/tonsillitis, and uncomplicated skin and skin structure infections [1].

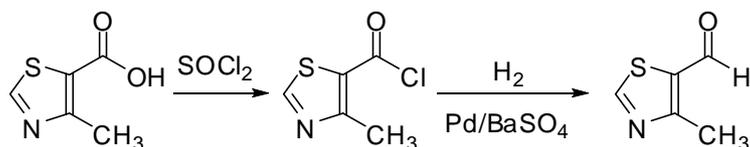
4-Methyl-5-formylthiazole (**b**, Figure 1) is a key intermediate for the synthesis of cefditoren pivoxil [2], which was first synthesized in 1939 [3]. The formation of the aldehyde group in this substance has been the focus of much research. Recently developed methods include the oxidation of 4-methyl-5-(2-hydroxyethyl)thiazole or 4-methyl-5-(hydroxymethyl)thiazole with MnO₂, CrO₃, or NaOCl [4-7] and the reduction of carboxylic ester with LiAlH₄, NaBH₄, or Red-Al [4,8-10]. However, these methods are eco-unfriendly and too expensive for industrial production. One reported better method is Cr-ZrO₂ catalyzed the gas phase hydrogenation of the corresponding carboxylic ester [11]. However, the

stability of product also causes difficulty in large scale production. We have found that Pd/BaSO₄ catalyzed hydrogenation of carboxylic chloride could give high yield and, moreover, be more eco-friendly and suitable for industrial production (Scheme 1).

Figure 1. Structure of cefditoren pivoxil and 4-methyl-5-formylthiazole.



Scheme 1. Synthesis of 4-methyl-5-formylthiazole.

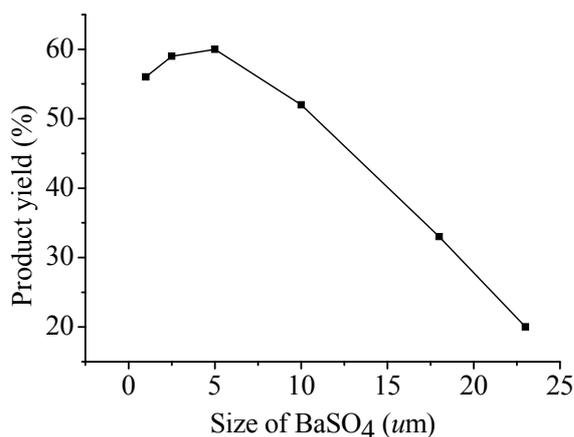


Results and Discussion

Effects of BaSO₄ particle size

We have found that nano-scale carbon can reduce the palladium content greatly while keeping good catalytic activity [12]. However, smaller nano-scale Pd/BaSO₄ may change its catalytic property due to nano-effects or congregation. Various BaSO₄ particles were tested while the Pd/BaSO₄ ratio (25% to acid) and palladium content (2.5%) were kept unchanged, as shown in Figure 2. The yield increased markedly along with the decrease of BaSO₄ size until the size of the BaSO₄ reached 5 μm. Subsequently, the yield decreased slowly.

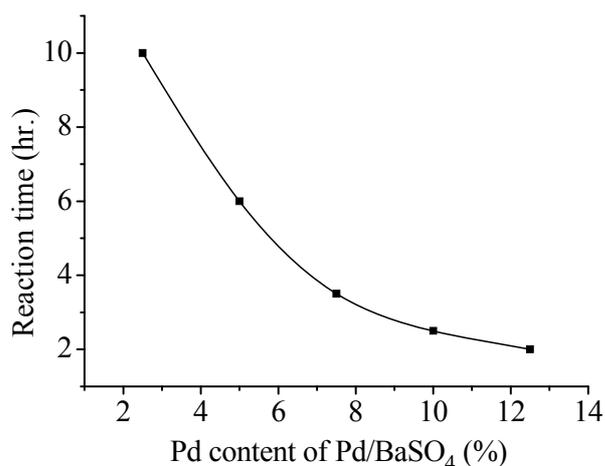
Figure 2 Effect of Pd/BaSO₄ size on product yield.



Effects of palladium content

Higher Pd content should have higher activity and make the reaction time shorter until the surface of the BaSO₄ is fully occupied. Based on above results, therefore, 5 μm-size BaSO₄ was used for checking the effects of palladium content. As the palladium content increased from 2.5%, the reaction time shortened linearly (Figure 3). An inflexion point was noted at 7.5% palladium content. Beyond that, additional palladium had little effect.

Figure 3. Effect of Pd content on reaction time.



Activation of the acyl chloride bond

The optimal temperature was 140°C. When TsOH, AlCl₃, BF₃, and FeCl₃ were added to activate the acyl chloride bond, adverse effects on the yield were found.

Conclusions

4-Methyl-5-formylthiazole can be efficiently prepared by Pd/BaSO₄ (5 μm, Pd: 7.5%) catalyzed hydrogenation of 4-methylthiazole-5-carboxylic chloride in xylene at refluxing temperature. This method is more eco-friendly and better suited for industrial production than previous methods.

Experimental

General

¹H-NMR and ¹³C-NMR spectra were recorded in CDCl₃ on a JEOL JNM-ECA300 spectrometer operating at 300 and 75 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, and coupling constants (*J*) are given in hertz (Hz). IR spectra were recorded on Nicolet AVATAR 360 FT-IR E.S.P. All reagents were purchased and used without further purification.

Catalyst Preparation

The Pd/BaSO₄ was prepared according to a literature method [13]. Various types of commercial BaSO₄ were used directly instead of this reagent being prepared *in situ*.

Synthesis of 4-methylthiazole-5-carboxylic acid chloride

4-Methylthiazole-5-carboxylic acid (1.5 g) was added to thionyl chloride (10 mL). After refluxing for 2 hours, the excess thionyl chloride was distilled off under reduced pressure. The remaining product was used directly for the next step without further purification.

General procedure for the synthesis of 4-methyl-5-formylthiazole

Xylene (30 mL) was added to the newly prepared carboxylic acid chloride. After the addition of Pd/BaSO₄ the mixture was heated to 140°C while hydrogen was passed into it. The reaction was monitored by TLC (petroleum ether-acetone = 3:1). When the reaction was finished, the mixture was filtered and extracted with 10% HCl (3×30 mL). The water solution was neutralized to pH = 8 with sodium carbonate and further extracted with chloroform (3×30 mL). After distillation of chloroform, pure product was obtained. ¹H-NMR (CDCl₃) δ: 10.1064 (s, 1H, -CHO), 8.9481 (s, 1H, 2-CH), 2.7571 (s, 3H, -CH₃); ¹³C-NMR (CDCl₃) δ: 182.4214 (1C, -CHO), 161.8374 (1C, 5-C), 158.8544 (1C, 2-CH), 132.8399 (1C, 4-C), 16.2193 (1C, -CH₃); IR (cm⁻¹, KBr): 3447 (m, w), 3091 (s), 2869 (s), 1660 (s), 1522 (s), 1409 (s), 1319 (s).

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