Communication

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

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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.](image)

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.](image)

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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*Sample availability*: Contact the authors.

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