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Article

The Efficient Synthesis of One Febuxostat Impurity

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Abstract: An efficient synthesis of a febuxostat impurity (impurity **1**) is described. Initial synthetic routes were hampered by poor regiocontrol during esterification, leading to challenging separations of mono-ester byproducts. By strategically reversing the alkylation and esterification steps in alternative route, side reactions were effectively suppressed, allowing the isolation of key intermediate **8** in 85.3% yield. Subsequent alkylation and a one-pot Suzuki coupling afforded the target impurity **1** in satisfactory overall yield. This practical route ensures a reliable supply of impurity **1** as a reference standard to support the quality control of febuxostat.

Keywords: febuxostat; impurity synthesis; one-pot suzuki coupling; quality control

1. Introduction

Febuxostat (Figure 1) is a potent non-purine, selective inhibitor of xanthine oxidase [1]. It was first approved by the U.S. Food and Drug Administration (FDA) in 2009 as a second-line treatment for chronic management of hyperuricemia in patients with gout [2]. Unlike the purine analogue allopurinol, febuxostat functions through a distinct mechanism. It binds tightly to both the reduced and oxidized forms of the xanthine oxidase enzyme, thereby effectively reducing the production of uric acid [3]. Its superior efficacy in lowering serum urate levels has established it as a crucial therapeutic option, particularly for patients intolerant or unresponsive to allopurinol [3–5]. The synthesis of febuxostat is constituted of multi steps. As other active pharmaceutical ingredients (APIs), safety and efficacy of febuxostat are profoundly influenced by the presence of process-related and degradation impurities. Therefore, a comprehensive understanding and strict control of these impurities are highly important for the pharmaceutical integrity and patient safety of febuxostat [6].

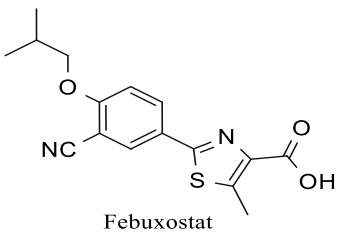


Figure 1. Structure of febuxostat.

To date, structures of about one hundred impurities related to febuxostat can be found online and in pharmacopeial standards [7,8]. Given that the synthesis of impurity reference standards is a prerequisite for rigorous analytical method development, our group has so far synthesized more than fifty of those impurities. The synthesis of one target compound, impurity **1** (Figure 2), was complicated by functional group incompatibility.

Specifically, the presence of two carboxylic acid groups introduced a challenging issue of regioselectivity during the esterification step. It is noted that Xu and coworkers once reported a two-step synthetic scheme (see Scheme 1) giving good selectivity and yields of impurity **1** even in the presence of two carboxylic acid groups [9]. However, our reproduction efforts were severely complicated by extensive di-esterification. The subsequent purification, requiring the separation of two closely related mono-esters (**1** and **2**, Figure 2) by column chromatography, proved to be particularly challenging. Therefore, a tactically designed synthetic route was necessary to minimize side reactions and secure a practical yield for impurity **1**.

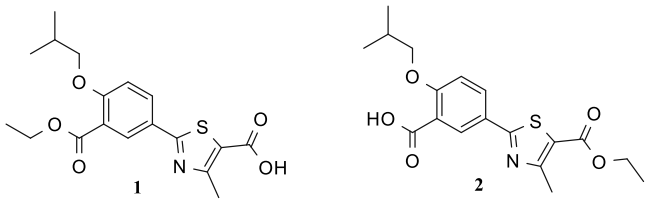
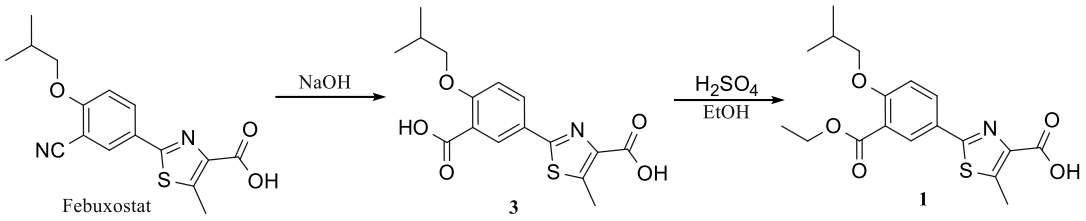


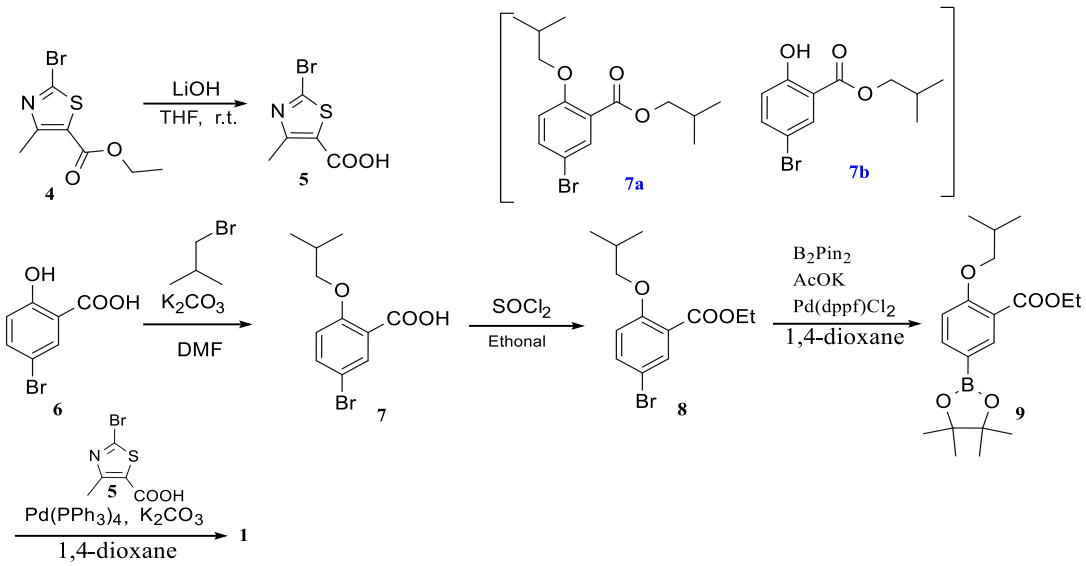
Figure 2. Structures of **1** and **2.**



Scheme 1. Xu's route of impurity **1.**

2. Results and Discussion

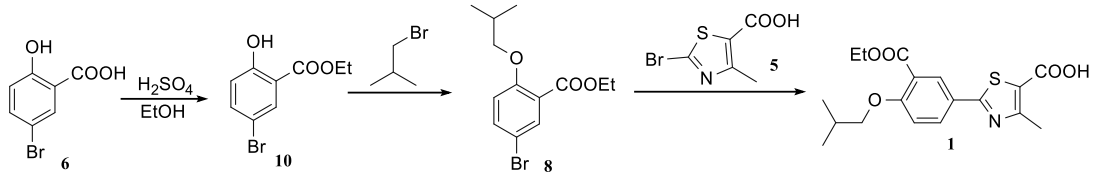
We then developed a 5-step synthesis method, and were able to obtain the target impurity **1** (see Scheme 2). However, the second step turned out to be problematic, leading to formation of large amount of esterification side products **7a** and **7b** (~30–40% based on TLC). The lack of selectivity, combined with the low atom economy of the route, finally prompted us to abandon this method.



Scheme 2. Alternative route of impurity **1.**

Following that, we revisited the 2nd and 3rd steps of Scheme 2. Simply reversing the order of these two steps, the aforementioned side reactions was effectively suppressed. Now, both steps give high yields of 91.0% and 85.3%, respectively (see Scheme 3). This is because step 3 of Scheme 2 involves an acid-catalyzed esterification

of the carboxylic acid group. When this step is performed first, the phenolic hydroxyl group remains inert. As a result, no side reactions occur, leading to a clean reaction system and a high yield of compound **10** (see Scheme 3). Subsequent alkylation under basic conditions afforded compound **8**. In this new route, we adapted a one-pot Suzuki coupling strategy from a previous study, which delivered the target impurity **1** directly from **5** and **8** with a satisfactory yield (64.4%).



Scheme 3. New route of impurity **1.**

3. Conclusions

In conclusion, an efficient synthetic route was developed for impurity **1**, one impurity of febuxostat. This route is consisted of esterification, alkylation, and finally, a one-pot Suzuki coupling, achieving an overall yield of 50.0%. This reliable access to impurity **1** will facilitate its procurement as a reference standard, thereby supporting rigorous quality control and regulatory compliance of febuxostat.

Experimental

Synthesis of compound **10**: To a solution of **6** (5.01 g, 23 mmol) in ethanol (150 mL) in a 250 mL single-neck flask was added a catalytic amount of concentrated sulfuric acid (0.5 mL). The mixture was stirred at 80 °C for 10 h. TLC showed the completion of the reaction, after which the mixture was cooled to ambient temperature and concentrated under reduced pressure. The colorless oil residue **10** (5.15 g, 91.0%) was used directly in the next step without further purification. MS: (ESI) *m*/*z*: 243.12 $[M-H]^-$.

Synthesis of compound **8**: To a solution of **10** (1.96 g, 8 mmol) in DMF (20 mL) were added K_2CO_3 (2.21 g, 16 mmol) and isobutyl bromide (2.21 g, 16 mmol). The mixture was stirred at 50 ℃ for 12 h. TLC showed the completion of the reaction, after which the mixture was cooled to ambient temperature. The mixture was filtered and concentrated under reduced pressure to give compound **8** (2.05 g, 85.3%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 2.6 Hz, 1H), 7.49 (dd, J = 8.9, 2.6 Hz, 1H), 6.80 (d, J = 8.9 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 3.75 (d, J = 6.4 Hz, 2H), 2.20–2.04 (m, 1H), 1.37 (t, J = 7.1 Hz, 3H), 1.04 (d, J = 6.7 Hz, 7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.27, 157.68, 135.68, 134.03, 122.43, 114.73, 111.86, 75.35, 61.10, 28.33, 19.14, 14.29.

Synthesis of impurity **1**: To a solution of **8** (1.50 g, 5 mmol) in dioxane:water (=50:10 mL) were added **5** (1.10 g, 5 mmol), CsF (4.50 g, 30 mmol), cataCXium A Pd G3 (728 mg, 1 mmol) and B_2Pin_2 (1.90 g, 7.5 mmol). The mixture was stirred at 85 °C under N_2 atmosphere overnight. TLC showed the completion of the reaction, after which the mixture was cooled to ambient temperature. The mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified on a silica gel column eluting with EA:PE (=3:1) to afford the desired product **1** as a white solid (1.17 g, 64.4%). MS: (ESI) *m*/*z*: 364.21 $[M+H]^+$, HPLC: 95.92%, ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.22 (d, J = 2.4 Hz, 1H), 8.08 (dd, J = 8.8, 2.4 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.90 (d, J = 6.7 Hz, 2H), 2.66 (s, 3H), 2.09–2.00 (m, 1H), 1.34–1.29 (t, J = 7.1 Hz, 3H), 1.01 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 167.24, 165.19, 162.87, 159.69, 159.52, 131.45, 128.67, 124.27, 122.21, 120.87, 113.89, 74.58, 60.78, 27.78, 18.80, 17.00, 14.10.

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Author Contributions

Writing—original draft, S.Z. and Z.Y.; writing—review and editing, S.Z. and Y.W. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

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