Process Development of Febuxostat Using Palladium- and Copper-Catalyzed C–H Arylation

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Abstract: There is significant interest in the development of process routes for active pharmaceutical ingredients using C–H arylation methodology. An efficient and practical synthetic route for febuxostat, which is the first non-purine-type xanthine oxidase inhibitor, was established via palladium- and copper-catalyzed C–H arylation of thiazole with aryl bromide. The catalyst loading was reduced to 0.1 mol % for the intermolecular C–H arylation, and a three-step synthesis produced febuxostat in 89% overall yield with excellent selectivity.

Keywords: febuxostat, xanthine oxidase inhibitor, palladium-copper-catalyzed, C–H arylation, regioselective

Introduction

Febuxostat (2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid, 1) was developed by Teijin Pharma Ltd. and approved as the first non-purine-type inhibitor of xanthine oxidase since allopurinol, which was approved more than 40 years ago.1 In patients with hyperuricemia and gout, the blood concentration of uric acid is higher than normal (~7.0 mg/dL), frequently resulting in acute joint pain from crystallized uric acid deposits. Febuxostat efficiently suppresses uric acid production by inhibiting xanthine oxidase, with a typical daily dose of 10–80 mg, in comparison with 100–800 mg of allopurinol. In addition, allopurinol requires dose reduction for patients with renal dysfunction, whereas febuxostat does not.2

Despite performing the same role, febuxostat has a chemical structure that is completely different from that of allopurinol (Figure 1), namely, a simple biaryl structure consisting of aryl and thiazole moieties and a non-purine structure.

Extensive synthetic efforts have been reported by several research groups. Li et al. reported a four-step linear synthesis of a febuxostat intermediate from commercially available 4-cyanophenol with an overall yield of 51%; this intermediate required two additional steps (such as isobutylation and hydrolysis) to synthesize febuxostat (eq 1 in Scheme 1).3 Alternatively, several convergent syntheses have also been reported. Itami et al. approached the synthesis using a three-step nickel-catalyzed C–H bond arylation reaction with an overall yield of 48% from 2-fluoro-5-iiodobenzoitrile, a relatively expensive starting material (eq 2 in Scheme 1).4 Togo et al. also developed synthetic routes (four or five steps) from less expensive starting materials such as 4-bromophenol, with overall yields between 23 and 31% (eq 3 in Scheme 1).5

The aforementioned syntheses achieved moderate to good yields and could be utilized to prepare other drug candidates. However, a more efficient and practical synthetic method is needed to enable the commercial-scale (hundreds of kilograms) manufacture of febuxostat. Herein we report our effort to develop an efficient and practical febuxostat synthesis using a palladium- and copper-catalyzed cross-coupling reaction via C–H bond activation.

Results and Discussion

We first focused on convergent synthetic routes rather than longer linear routes. Febuxostat can be selectively synthesized through traditional transition-metal-catalyzed cross-coupling reactions such as the Negishi and Suzuki couplings.6 However, the classical cross-couplings (i) require unnecessary steps to introduce functional groups such as a zinc (hetero)aryl halide or (hetero)aryl boronic acid and (ii) generate massive amounts of waste derived from these unnecessary functional groups, even though the reactions themselves are catalytic. To resolve these issues by developing a process that upholds the principles of green chemistry, we chose to investigate intermolecular C–H bond arylation.

Itami et al.7 reported that nickel-catalyzed C–H arylation produces a concomitant byproduct, such as the thiazole dimer to generate Ni0 species from NiII species, that can influence the purity of the active pharmaceutical ingredient (API). Therefore, to meet product specifications, we focused on developing a process that, in addition to being efficient and practical, affords excellent selectivity and purity.

We began our study with a survey of various transition-metal catalyst species, including nickel,6 copper,8 cobalt,9 iron,10 ruthenium,11 and palladium.12 After catalyst screening for C–H bond arylation of the thiazole moiety (3a) with aryl bromide 2, we found that palladium served as an efficient catalyst in the presence of various ligands. Moreover, electron-rich and bulky...
phosphine ligands such as di-tert-butyl(cyclohexyl)phosphine (tBu2PCy) gave good results, affording the coupling product 4a in 91% isolated yield after silica gel purification (Scheme 2). The ligand is liquid at room temperature and relatively stable when stored under an inert atmosphere. Therefore, it is easier to handle than other well-known ligands such as tri-tert-butylphosphine and tricyclohexylphosphine. The aforementioned result encouraged us to reduce the catalyst quantity.

Table 1. Evaluation of Additives

<table>
<thead>
<tr>
<th>entry</th>
<th>Pd (mol %)</th>
<th>mol % tBu2PCy</th>
<th>additive (mol %)</th>
<th>conversion (%)&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>4b</th>
<th>5</th>
<th>6</th>
<th>7a + 7b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt; (0.5)</td>
<td>1.2</td>
<td>-</td>
<td>66.0</td>
<td>61.5</td>
<td>0.8</td>
<td>0.7</td>
<td>3.0</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt; (0.5)</td>
<td>1.2</td>
<td>PivOH (2.0)</td>
<td>96.7</td>
<td>78.5</td>
<td>1.8</td>
<td>1.9</td>
<td>14.6</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt; (0.25)</td>
<td>0.60</td>
<td>-</td>
<td>33.3</td>
<td>31.9</td>
<td>0.2</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt; (0.25)</td>
<td>0.60</td>
<td>PrCO&lt;sub&gt;2&lt;/sub&gt;H (1.0)</td>
<td>44.1</td>
<td>41.9</td>
<td>0.0</td>
<td>0.7</td>
<td>1.4</td>
</tr>
<tr>
<td>5</td>
<td>PdCl&lt;sub&gt;2&lt;/sub&gt; (0.25)</td>
<td>0.60</td>
<td>PrCO&lt;sub&gt;2&lt;/sub&gt;H (1.0)</td>
<td>57.7</td>
<td>54.2</td>
<td>0.0</td>
<td>0.7</td>
<td>2.8</td>
</tr>
<tr>
<td>6</td>
<td>PdCl&lt;sub&gt;2&lt;/sub&gt; (0.25)</td>
<td>1.0</td>
<td>-</td>
<td>77.2</td>
<td>70.1</td>
<td>0.1</td>
<td>0.9</td>
<td>6.2</td>
</tr>
</tbody>
</table>

<sup>a</sup>Conversion (%) = 100% − area % of 2.<sup>c</sup>The HPLC area % of 2, 4b, 5, 6, 7a, and 7b was integrated as the total became 100%. Observed at 240 nm. <sup>c</sup>Reaction for 4 h.
which affects the manufacturing cost and the residual palladium content in the API.

With the effective ligand \( \text{tBu}_2\text{PCy} \) in hand, we next evaluated the role of additives under conditions of higher concentration (4 v/w) and reaction temperature (140 °C) on the basis of preliminary knowledge that these conditions result in higher product conversion than the aforementioned conditions (13 v/w, 120 °C). Additionally, we changed the thiazole moiety to ethyl ester 3b from \( \text{tBu}^-\text{butyl ester} \) 3a to simplify the subsequent hydrolysis.

When the catalyst amount was decreased from 10 to 0.5 mol % in the absence of additives, only moderate reaction conversion (66.0%) was achieved under the new conditions (Table 1, entry 1). As Fagnou reported,13 the addition of pivalic acid accelerated the reaction conversion at the expense of substrate selectivity \((7a + 7b = 14.6 \text{ area } \% \)) (entry 2). We assumed that the highly activated palladium catalyst coordinated to the thiazole part of the coupling product (4b), resulting in over-reaction with the remaining aryl bromide 2 to give 7a and 7b. Further reduction of the catalyst loading to half the amount (0.25 mol %) gave lower reaction conversion but better substrate selectivity (entry 3). We subsequently evaluated several dozen carboxylic acids to facilitate the reaction. Although the reactivity was similar among them, isobutyric acid was found to be slightly more effective than pivalic acid, isobutyric acid was evaluated more e ective than the aforementioned conditions (entry 4). Furthermore, because the melting point of isobutyric acid is lower than that of pivalic acid, isobutyric acid can be used without a preheating step, which is a handling benefit.

Palladium species were then surveyed. We hypothesized that acetic acid on Pd(OAc)\(_2\) could potentially prevent the coordination of isobutyric acid to palladium. Although the effect was not as pronounced as we expected, we selected PdCl\(_2\), which gave a moderate conversion rate (57.7%) (entry 5).

Finally, the reaction conversion was improved (77.2%) through optimization of the palladium-to-ligand ratio (entry 6). However, the starting material 2 was not fully consumed, and impurities 7a and 7b were generated at an unacceptable level (6.2 area %).

To solve the aforementioned issues, we evaluated supplementary additives in the presence of the carboxylic acid. After extensive investigation, we found that a copper salt such as CuBr-SMe\(_2\) functioned as a cocatalyst, dramatically decreasing the impurity concentrations (Table 2, entry 1). We assumed that the copper salt enhanced the coupling reactivity by serving as a Lewis acid to the thiazole-ring heteroatom and changing the electron density, thereby activating the C–H bond at C2 of the thiazole. As evidence supporting our speculation, we found that all of the reagents were necessary and impurities 7a and 7b were generated at an unacceptable level (entry 6).

Table 2. Role of Reagents for C–H Arylation

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>conversion (%)(^{a,b})</th>
<th>4b</th>
<th>5</th>
<th>6</th>
<th>7a + 7b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>added all</td>
<td>100</td>
<td>98.2</td>
<td>0.2</td>
<td>0.4</td>
<td>1.1</td>
</tr>
<tr>
<td>2</td>
<td>without PdCl(_2)</td>
<td>0.5</td>
<td>0.5</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>3</td>
<td>without CuBr-SMe(_2)</td>
<td>66.0</td>
<td>62.2</td>
<td>0.0</td>
<td>1.0</td>
<td>2.9</td>
</tr>
<tr>
<td>4</td>
<td>without (\text{tBu}_2\text{PCy})</td>
<td>14.3</td>
<td>13.0</td>
<td>0.3</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>5</td>
<td>without PrCO(_2)H</td>
<td>7.8</td>
<td>7.3</td>
<td>0.0</td>
<td>0.6</td>
<td>0.0</td>
</tr>
<tr>
<td>6</td>
<td>without K(_2)CO(_3)</td>
<td>0.6</td>
<td>0.1</td>
<td>0.0</td>
<td>0.5</td>
<td>0.0</td>
</tr>
</tbody>
</table>

\(^{a}\)Conversion (%) = 100% − area % of 2. \(^{b}\)The HPLC area % of 2, 4b, 5, 6, 7a, and 7b was integrated as the total became 100%. Observed at 240 nm.

Three or more reaction mechanisms have been reported for C–H arylation.14 However, to our knowledge, the detailed mechanism of C–H arylation using a cocatalytic system of palladium species, a carboxylic acid, and a copper salt has not been reported. Furthermore, a detailed mechanistic study has yet to be performed. Thus, the precise mechanism remains unclear.

The final optimization showed that K\(_2\)CO\(_3\) was preferable to K\(_3\)CO\(_3\), allowing the catalyst loading to be reduced to 0.1 mol % and the reaction temperature to be lowered from 140 to 120 °C. Furthermore, inexpensive CuBr and toluene were applicable, instead of CuBr-SMe\(_2\) and xylene. Thus, we successfully developed an efficient and practical process route to febuxostat via C–H arylation (Scheme 3). The telescoped
process of isobutoxylation and C–H arylation was achieved in 91% yield over two steps from commercially available 5-bromo-2-fluorobenzonitrile (8). The final hydrolysis proceeded without difficulty, and febuxostat with greater than 99% HPLC purity was obtained in 89% overall yield in three steps.

Table 3 shows a comparison of our process and previously reported methods. As shown, our process is more effective and productive than the previously reported methods.

### Table 3. Comparison of Synthetic Processes for Febuxostat

<table>
<thead>
<tr>
<th>major author</th>
<th>no. of steps</th>
<th>overall yield (%)</th>
<th>starting material(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li</td>
<td>3</td>
<td>≤51</td>
<td>4-cyanophenol</td>
</tr>
<tr>
<td>Itami</td>
<td>3</td>
<td>48</td>
<td>2-fluoro-5-isobutoxybenzonitrile</td>
</tr>
<tr>
<td>Togo</td>
<td>4–5</td>
<td>23–31</td>
<td>4-bromophenol</td>
</tr>
<tr>
<td>this work</td>
<td>3</td>
<td>89</td>
<td>5-bromo-2-fluorobenzonitrile</td>
</tr>
</tbody>
</table>

**CONCLUSION**

We successfully developed an efficient and practical synthetic route for febuxostat via C–H arylation in combination with palladium and copper catalysis. The palladium catalyst loading was reduced to as low as 0.1 mol %, with febuxostat synthesized in 89% overall yield in three steps from commercially available 5-bromo-2-fluorobenzonitrile. Currently, we are focusing on establishing a scalable manufacturing process. Further modifications and engineering efforts are underway to enhance the robustness against catalyst poisoning in the thiazole material, reduce the residual metals in the API, shorten the reaction time, clarify the role of the copper source, etc. These efforts will be discussed in a future paper.

**EXPERIMENTAL SECTION**

**General.** All of the reactions were carried out under a N₂ atmosphere. Compound 3a was synthesized using a previously reported method. All of the commercial chemicals were used as received. For purification, flash column chromatography (Biotage Flash, Si40) was used. The reactions were monitored by reversed-phase HPLC (G1315A Hewlett-Packard series 1100) under the following conditions: Column: Phenomenex Luna phenyl-hexyl column (5 μm, 4.6 mm × 100 mm), Eluent: (A) 5% MeCN/95% H₂O + 0.05% TFA; (B) 95% MeCN/5% H₂O + 0.05% TFA. Gradient: 1 min pretime at 10% B, linear ramp from 10% to 70% B over 13 min, linear ramp from 70% to 80% B over 10 min, linear ramp from 80% to 100% B over 1 min, hold at 100% B for 5 min, linear ramp from 100% to 10% B over 2 min, and then 3 min post-time at 10% B. Flow rate: 1.0 mL/min. UV detection: 240 nm. ¹H NMR spectra were recorded on a JEOL JNM-AL-400 spectrometer.

**First-Generation C–H Arylation (Scheme 2). tert-Butyl 2-(3-Cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylate (4a).** To a three-neck flask, 3a (598 mg, 3.0 mmol), Pd(OAc)₂ (67 mg, 0.30 mmol), di-tert-butyl(cyclohexyl)phosphine (137 mg, 0.60 mmol), K₂CO₃ (829 mg, 6.0 mmol), and toluene (10 mL) were added under N₂. The mixture was stirred at the reflux temperature for 24 h and subsequently cooled to room temperature, followed by the addition of water (15 mL) and ethyl acetate (20 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (20 mL). The combined organic layer was dried over MgSO₄ and concentrated under reduced pressure. To the resulting solid were added toluene (1 mL) and heptane (9 mL). The mixture was warmed to 70 °C and then cooled to 0 °C. The resulting slurry was filtered, and the wet cake was washed with heptane (20 mL) and then dried in vacuo. The filtrate was concentrated and purified by silica gel
column chromatography (hexane/ethyl acetate = 100/0 to 0/100) to yield 4a (611 mg from the solid and 405 mg from the filtrate; 91% yield in total) as an off-white solid. The NMR spectrum was consistent with that reported previously.4

Second-Generation C–H Arylation: Reaction Screening (Table 1). Ethyl 2-(3-Cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylate (4b). To a three-neck flask, 3b (1.71 g, 10.0 mmol), di-tert-butyl(cyclohexyl)phosphine, additive, K2CO3 (2.90 g, 21.0 mmol), and xylene (10 mL) were added under reduced pressure. N2 was then back-filled into the vessel, to a three-neck flask, 3b (1.71 g, 10.0 mmol), di-tert-butyl(cyclohexyl)phosphine, additive, K2CO3 (2.90 g, 21.0 mmol), and/or xylene (7.5 mL) were added under reduced pressure. N2 was then back-filled into the vessel, the mixture was stirred at the same temperature for 1 h, cooled to 60 °C, inducing precipitation. The mixture was filtered, and the wet cake was washed with warm 80% aqueous EtOH (76 mL) and the wet cake was washed with warm 80% aqueous EtOH (76 mL) and the wet cake was washed with warm 80% aqueous EtOH (76 mL) and the wet cake was washed with warm 80% aqueous EtOH (76 mL). The mixture was filtered, and the wet cake was washed with warm 80% aqueous EtOH (76 mL) and the wet cake was washed with warm 80% aqueous EtOH (76 mL) and the wet cake was washed with warm 80% aqueous EtOH (76 mL).

C–H Arylation: Role of the Reagents (Table 2). Ethyl 2-(3-Cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylate (4b). N2 was vigorously flowed into a sealed tube, to which 3b (2.14 g, 12.5 mmol), 2 (2.54 g, 10.0 mmol), PdCl2 (4.4 mg, 0.025 mmol), di-tert-butyl(cyclohexyl)phosphine (22.8 mg, 0.10 mmol), isobutyratic acid (8.8 mg, 0.10 mmol), copper(I) bromide—dimethyl sulfoxide complex (206 mg, 1.00 mmol), K2CO3 (2.90 g, 21.0 mmol), and/or xylene (7.5 mL) were added. The tube was quickly closed, and the mixture was stirred in an aluminum block at 140 °C for 24 h. CAUTION! The internal pressure greatly increases because of CO2 and water evolution! The mixture was diluted and measured by HPLC.

Optimized C–H Arylation: Ethyl 2-(3-Cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylate (4b). To a mixture of potassium tert-butoxide (11.8 g, 105 mmol) and toluene (100 mL) was added 2-methyl-1-propanol (8.15 g, 110 mmol) dropwise as the internal temperature of 90 °C. To the solution of 3b (18.0 g, 105 mmol), PdCl2 (18 mg, 0.10 mmol), di-tert-butyl(cyclohexyl)phosphine (22.8 mg, 0.10 mmol), isobutyratic acid (8.8 mg, 0.10 mmol), copper(I) bromide—dimethyl sulfoxide complex (206 mg, 1.00 mmol), K2CO3 (2.90 g, 21.0 mmol), and/or xylene (7.5 mL) were added. The tube was quickly closed, and the mixture was stirred in an aluminum block at 140 °C for 24 h. CAUTION! The internal pressure greatly increases because of CO2 and water evolution! The mixture was diluted and measured by HPLC.

To the solution of 2 in a three-neck flask with a Dean–Stark trap16 were added 3b (18.0 g, 105 mmol), PdCl2 (18 mg, 0.10 mmol), di-tert-butyl(cyclohexyl)phosphine (55 mg, 0.24 mmol), isobutyratic acid (35 mg, 0.40 mmol), copper(I) bromide (143 mg, 1.00 mmol), KHCO3 (210 g, 210 mmol), and toluene (23 mL, in addition to the aforementioned 53 mL) under N2. After 5 min of stirring at room temperature, the mixture was warmed and stirred at the reflux temperature for 15 h. After reaction completion, the mixture was cooled to an internal temperature of 90 °C. The insoluble species were then filtered off (remaining at this temperature) and washed with hot toluene (25 mL). The filtrate was then partially concentrated at 60 °C under reduced pressure. To the concentrated mixture (53 mL of toluene was assayed), additional toluene (23 mL) and 90% aqueous EtOH (178 mL) were added. The mixture was dissolved at 85 °C and then cooled to 60–68 °C, inducing precipitation. The mixture was stirred at the same temperature for 1 h, cooled to 0 °C over 2 h, and stirred at 0 °C for 1.5 h. The resulting slurry was filtered, and the wet cake was washed with 80% aqueous EtOH (76 mL) and dried in vacuo at 80 °C to give 4b (31.3 g, 91%) as a whitish solid.1H NMR (400 MHz, CDCl3): δ 8.18 (d, J = 2.4 Hz, 1H), 8.09 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H), 3.90 (d, J = 6.4 Hz, 2H), 2.77 (s, 3H), 2.23–2.19 (m, 1H), 1.39 (t, J = 7.2 Hz, 3H), 1.09 (d, J = 6.8 Hz, 6H).

2-(3-Cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic Acid (Febuxostat, 1). To a three-neck flask were added 4b (25.0 g, 72.6 mmol), THF (25 mL), and ethanol (175 mL). The mixture was warmed to 40–50 °C, and 8 N aqueous NaOH (10.9 mL, 87.1 mmol) was added to the mixture. The mixture was stirred at the same temperature until the conversion reached 99.5%. Water (76.2 mL) was added to the mixture, and the resulting mixture was stirred for 1 h at the same temperature, followed by quenching with 1 M aqueous HCl (95.8 mL, 95.8 mmol) to adjust the pH to below 3.5. To the mixture was added water (62.5 mL) at 60–70 °C, and the resulting mixture was then heated to the reflux temperature, stirred for 30 min, and cooled to 30–40 °C. The resulting slurry was filtered, and the wet cake was washed with warm water (625 mL) and dried in vacuo at 75–85 °C to give 1 (22.5 g, 98%) as a whitish solid.1H NMR (400 MHz, CDCl3): δ 8.20 (d, J = 2.4 Hz, 1H), 8.11 (dd, J = 9.0 Hz, 2.4 Hz, 1H), 7.03 (d, J = 9.0 Hz, 1H), 3.91 (d, J = 6.6 Hz, 2H), 2.80 (s, 3H), 2.23–2.20 (m, 1H), 1.20 (d, J = 6.8 Hz, 6H).

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■ REFERENCES


