A Flow-Based Synthesis of Telmisartan

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A highly efficient continuous synthesis has been developed for telmisartan, the active ingredient in the antihypertensive drug, Micardis. This synthetic route employs a convergent strategy that requires no intermediate purifications or solvent exchanges. The key step in the reaction scheme is a Suzuki cross-coupling reaction between two functionalized benzimidazoles that is catalyzed by a solid-supported Pd catalyst. This flow-based approach utilizes a tubular reactor system coupled with a plug flow packed bed cartridge unit that produces telmisartan in an 81% isolated yield.

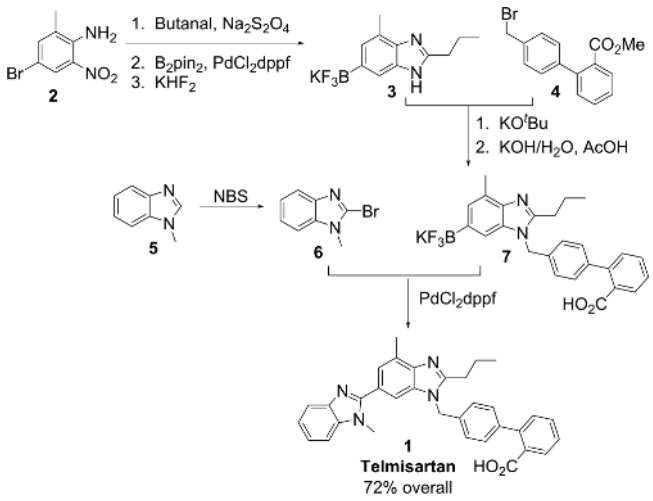
Keywords: telmisartan, Suzuki reaction, flow chemistry, palladium, benzimidazole

1. Introduction

High blood pressure is a major risk factor for cardiovascular disease and has been implicated in 16.5 % of all deaths [1]. Telmisartan (**1**) is an antihypertensive drug currently marketed under the brand name Micardis® [2]. It acts as an angiotensin receptor antagonist and is one of the most efficacious drugs in its class, with the longest half-life, a high-protein binding affinity, and a low daily dosage [3]. Telmisartan has also been shown to provide additional benefits against vascular and renal damage caused by diabetes and cardiovascular disease [4]. It has been suggested that it may prevent cognitive decline in Alzheimer's disease as well [5]. Telmisartan recently lost patent protection in the US, so the development of a continuous-flow process for its synthesis is now timely.

Previous methods for the preparation of telmisartan [6] employed a common synthetic strategy in which the functionalized dibenzimidazole precursors are assembled through sequential cyclization reactions followed by the addition of the biphenyl moiety. These approaches require numerous intermediate isolations to purge byproduct impurities from low yielding reactions, adding a significant level of process complexity and waste to the overall process. We recently reported a new strategy that offers a convergent preparation of telmisartan whereby the dibenzimidazole component is prepared using a Suzuki reaction between two separate functionalized benzimidazoles (Scheme 1) [7]. Starting with 4-bromo-2-methyl-6-nitroaniline (**2**), the central benzimidazole fragment (**3**) is formed over three steps. The biphenyl moiety is introduced via an *N*-alkylation between compounds **3** and **4**, and the methyl ester is then deesterified to the carboxylic acid **7**. Selective bromination of 1-methylbenzimidazole (**5**) at the 2-position provides the other benzimidazole fragment (**6**). To complete the synthesis, a Suzuki cross-coupling reaction between advanced intermediates **6** and **7** yields the target molecule. This process generates telmisartan in a 72 % overall yield over 6 steps. We now report the application of our convergent strategy to a similarly high-yielding continuous synthesis of telmisartan.

Scheme 1. Batch preparation of telmisartan



We postulated that the final three chemical transformations from our batch process would be ideal candidates for conversion to a flow based approach for the following reasons: (1) all three steps can be achieved in high yields with relatively short reaction times, (2) all three steps are performed under basic conditions, and (3) a compatible solvent system could be used that would preclude solvent exchanges or intermediate isolations. Using this strategy, we developed a three-step continuous-flow preparation of telmisartan, with no isolated intermediates. The target molecule is assembled from two different functionalized benzimidazole fragments (**3** and **6**) and the biphenyl moiety **4**, by performing the alkylation, saponification, and Suzuki reactions under continuous-flow conditions.

2. Results and Discussion

Since our previously reported batch process [7], we have developed a more efficient and economically viable approach to the preparation of the central benzimidazole component (**3**). This streamlined method uses 4-bromo-2-methyl-6-nitroaniline (**2**) as a starting material, and the functionalized benzimidazole **3** is assembled avoiding isolation of intermediates (Scheme 2). The benzimidazole ring is formed via a reductive cyclization reaction between **2** and butyraldehyde [8]. This reaction is completed in 5 h under reflux with a 1:1 water–methanol mixture using sodium dithionite as the reductant. The boron species is then inserted at the 6-position of the benzimidazole. We elected to use diboronic acid [9] in order to improve the overall atom economy of this procedure. We were able to complete the transformation with a more cost effective catalyst ($PdCl_2(PPh_3)_2$) while reducing the catalyst loading to 3 mol%. The boronic acid is converted to trifluoroborate salt **3** with potassium bifluoride. The salt is easily isolated in an overall yield of 90 % from **2**.

We next sought out a compatible solvent system that would preclude solvent exchanges or intermediate isolations. Our original ethanol–water system from the batch process proved to be problematic and unacceptable for processing in flow. We found that

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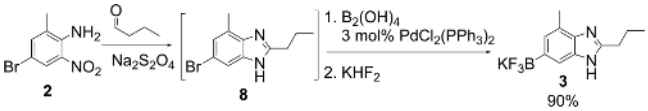
Scheme 2. Preparation of compound **3**



replacing the ethanol–water with a mixture of *N*-methylpyrrolidone (NMP) and water gave a good combination of high reactivity and improved solubility, thus, avoiding solid formation during the sequence of reactions.

The alkylation and deesterification steps were performed in a Vapourtec E-Series system with two 10 mL TFA reactor coils (Scheme 3). In the first reaction stream, benzimidazole **3** and potassium *tert*-butoxide are premixed in NMP. This initial mixing allows for deprotonation of the 1-position of the benzimidazole, improves solubility of the trifluoroborate salt, and helps to avoid formation of the unwanted Williamson ether byproducts when the biphenyl moiety is introduced. The second reaction stream contains a solution of bromide **4** in NMP. The solution streams are mixed together and fed into the first reactor coil and heated at 100 °C with an estimated residence time of 20 min. An excess of potassium hydroxide in water is added to the outlet from the first coil, which is then introduced into a second reactor coil. This combined mixture is then fed to the second coil and heated to 120 °C with an approximate residence time of 10 min, which results in complete hydrolysis of the methyl ester. The pressure of the system was maintained between 4 and 5 bar during the deesterification step. These two chemical transformations provide a 97 % conversion to alkylated benzimidazole **7**.

With the first two continuous transformations completed, we then directed our efforts to the development of continuous conditions for the Suzuki cross-coupling reaction. A commercially available silica supported palladium, SiliaCat® DPP-Pd, was used to carry out the reaction, which was performed in a ThalesNano X-Cube flow reactor. The outlet stream from the previous two steps was collected in a reservoir and then introduced to a solution containing 1.2 equivalents of 2-bromo-1-methylbenzimidazole in 1:1 NMP–H_2O (Scheme 3). Optimized conditions were established when the catalyst bed was heated to 180 °C, and the reaction mixture was passed through the column at a flow rate of 0.1 mL/min at 40 bar. The estimated residence time under these conditions was less than 5 min. When the three steps were consolidated into a single continuous process, an overall isolated yield of 81 % was achieved.

3. Conclusion

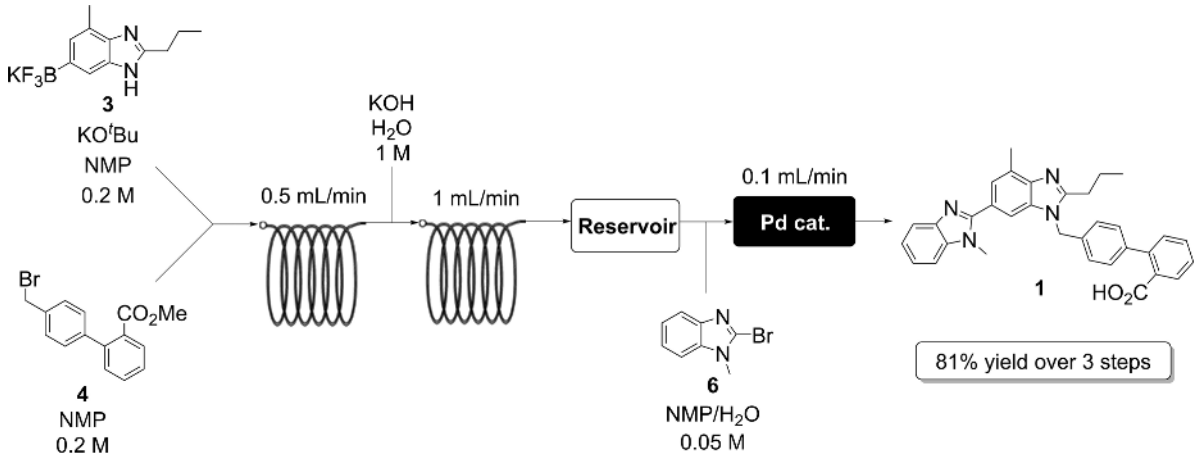
We have demonstrated a flow-based synthesis of telmisartan which employs a highly efficient convergent strategy that requires no intermediate purifications or solvent exchanges. The process features a Suzuki cross-coupling reaction catalyzed by a solid supported Pd catalyst that produces the desired product with an 81 % yield in flow. This continuous approach represents a significant improvement over existing methods that require numerous additional unit operations that add complexity and waste to the overall process. From a broader perspective, dibenzimidazoles represent an important class of pharmacophores, and this flow-based method may serve as a selective and straightforward alternative for the continuous preparation of these privileged structures.

4. Experimental

4.1. Preparation of Compound 3. 6-Bromo-4-methyl-2-propylbenzimidazole (**2**) (2.0 g, 8.7 mmol) and butyraldehyde (1.6 mL, 17.3 mmol) were added to a flask along with sodium dithionite (7.5 g, 43.2 mmol) and 40 mL of 50 % MeOH in H_2O. The mixture was stirred at reflux for 5 h. The MeOH was removed by rotary evaporator. An additional 20 mL of H_2O was added to the remaining aqueous solution and was then extracted using DCM (3 × 50 mL). The organic layer was concentrated by rotary evaporator and then taken up in 80 mL of EtOH. The solution was added to a flask containing diboronic acid (2.3 g, 26.0 mmol), KOAc (2.5 g, 26.0 mmol), $PdCl_2(PPh_3)_2$ (182 mg, 0.26 mmol), and triphenylphosphine (91 mg, 0.35 mmol). The flask was then evacuated and placed under nitrogen. The solution was heated at 75 °C for 10 h. The reaction mixture was cooled, filtered, and then concentrated by rotary evaporator followed by the addition of 80 mL of H_2O. The aqueous mixture was then extracted with EtOAc (3 × 100 mL). The organic layer was combined and concentrated to about 100 mL. The remaining solution was then combined with a solution of potassium bifluoride (3.4 g, 43.3 mmol) in H_2O. The biphasic mixture was stirred at room temperature for 5 h. The precipitate was filtered, rinsed using THF, and then dried, yielding **3** as a white solid (2.2 g, 90 %).

4.2. Procedure for Flow Reactions. A mixture of **3** (1 equiv., 0.2 M) and KOtBu (3 equiv.) in NMP was stirred in the first inlet reservoir. A second inlet solution containing **4** (1 equiv., 0.2 M) in NMP was prepared, and each was pumped at 0.25 mL/min through a T-joint into a Vapourtec E-series. The reaction mixture was flowed through a 10-mL reactor coil at 100 °C. Directly after the first coil, a third pump introduced a third solution containing aqueous KOH (10 equiv., 1 M) at 0.5 mL/min. The combined stream was pumped into a second 10 mL reactor coil at 120 °C. The outlet was collected in a reservoir then combined with a fourth solution containing bromobenzimidazole **6** (1.2 equiv., 0.05 M) in

Scheme 3. Three-step continuous-flow synthesis of telmisartan



a 50/50 mixture of NMP–H_2O. This combined stream was then pumped into a ThalesNano X-cube at 0.1 mL/min through a cartridge containing 100 mg of catalyst (SiliaCat® DPP-Pd) kept at 180 °C. The final outlet was collected (2 mL, 20 min) and diluted 4x with H_2O and acidified using AcOH. The resulting precipitate was filtered and stirred in chloroform. The remaining solid was discarded, and the chloroform was removed by rotary evaporator. The residue was taken up in a dilute aqueous KOH solution and acidified using AcOH. The precipitate was filtered and dried to produce **1** (20.7 mg, 81 % yield, 97 % purity by HPLC), corresponding to a production rate of 1 mg/min.

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