ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

pubs.acs.org/OPRD

Article

Highly Efficient and Practical Synthesis of the Key Intermediate of Telmisartan

Jianhong Zhao,* Yicheng Xiong, Wu-Lin Yang, Fan Yang, and Yu Jin

Cite This: *Org. Process Res. Dev.* 2021, 25, 1022−1027

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: We reported herein an efficient and practical method to access 1,7′-dimethyl-2′-propyl-2,5′-bi(1*H*-benzimidazole) **1**, a key intermediate for the synthesis of telmisartan. The synthetic route was based on readily available *o*-methylaniline as the starting material, and the target product **1** was prepared through a six-step process, including amidation, formylation, cyclization, hydrolysis, amidine, and oxidation. The overall yield for the preparation of **1** was 51.5% on the 100 g scale, with a purity of 99.91%. The salient features of this method include economic and easily available starting materials, operational simplicity, and environmentally friendly, which is suitable for the industrial production.

KEYWORDS: *Telmisartan, practical synthesis, 1,7′-dimethyl-2′-propyl-2,5′-bi(1H-benzimidazole), Duff reaction, benzimidazole*

1. INTRODUCTION

Telmisartan, a highly selective angiotensin II receptor antagonist, was approved by the FDA as an effective antihypertensive drug in 1998, which had the advantages of maintaining the normal regulation function of the cardiovascular system and reducing the organ damage caused by hypertension.[1,2] Notably, telmisartan was one of the top-selling antihypertensive drugs on the market due to the excellent effect, low toxicity, and once-daily dosage.[3]

Considering that 1,7′-dimethyl-2′-propyl-2,5′-bi(1*H*-benzimidazole) **1** was the key intermediate for the synthesis of telmisartan (Figure 1), numerous methods have been reported for the preparation of compound **1**, among which three methods enabled manufacturing of **1** in large scale.[4,5]

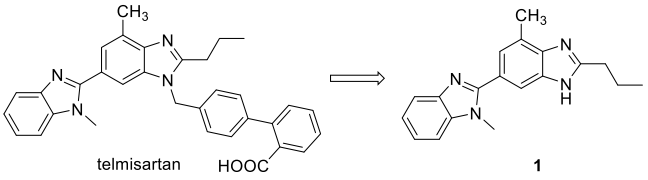
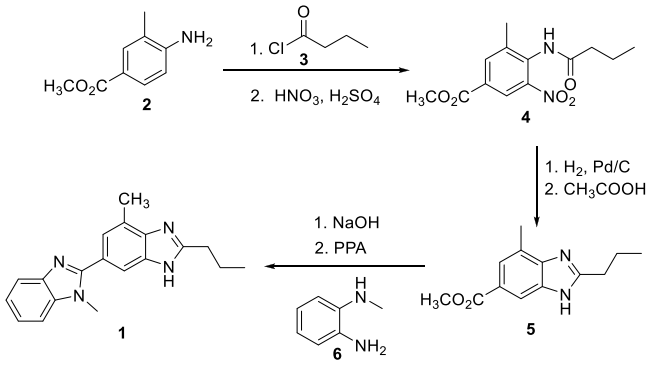


Figure 1. Structure of telmisartan.

The first generation synthetic route to intermediate **1** was introduced by Ries,[5] as shown in Scheme 1, which adopted 4-amino-3-methylbenzoic acid methyl ester **2** as the raw material, through amidation, mixed acid nitration, reduction of the nitro group, and cyclization of the resulting amine to give benzimidazole derivative **5**. Subsequent saponification of **5** followed by condensation with *N*-methyl-1,2-phenylenediamine **6** in the presence of polyphosphoric acid (PPA) at elevated temperature (150 °C) afforded target intermediate **1**. However, this protocol suffered from the use of expensive raw material and dangerous or costly reagents including mixed acid for nitration, flammable palladium−carbon (Pd/C), and excess

Scheme 1. Original Routes for the Synthesis of Key Intermediate 1



PPA for cyclization as dehydrating agent and solvent, thus resulting in the complex operation, increased potential safety hazard, high production cost, and serious environmental pollution.

In this context, improvements to the process were successively reported. For instance, Reddy[6] improved the yield slightly by optimizing the reaction conditions and operation. However, the elevated temperature and acidic conditions were still required during the final cyclization step. In addition, by using *o*-methylphenol as the starting material, Wang[7] synthesized target compound **1** via the cyclocondensation of aldehyde with *o*-nitroanilines or *o*-phenylenediamine as the construction of key benzimidazoles, which

Received: January 21, 2021
Published: March 17, 2021

https://doi.org/10.1021/acs.oprd.1c00025
Org. Process Res. Dev. 2021, 25, 1022−1027

Scheme 2. Improved Process for the Synthesis of the Key Intermediate 1

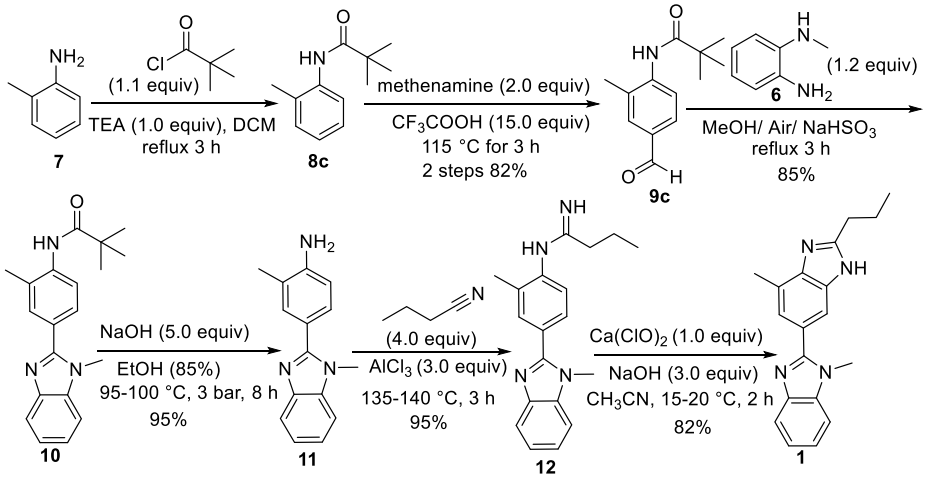
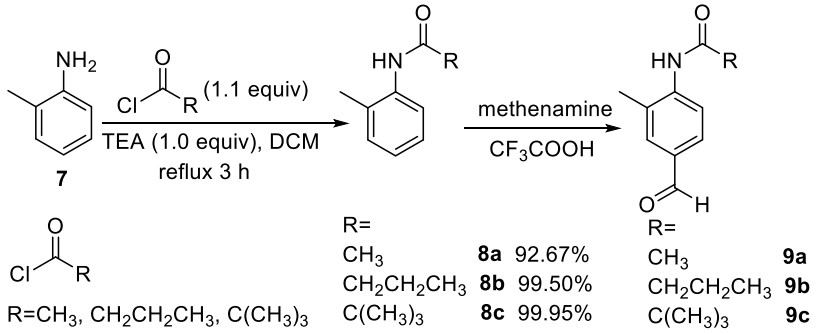


Table 1. Optimization of Conditions for the Duff Reaction[a]



entry	R	methenamine (equiv)	trifluoroacetic acid (equiv)	temp (°C)[b]	yield (%)[c]
1[d]	*t*-Bu	3	5	75	NR
2[d]	*t*-Bu	3	5	110	30
3[d]	*t*-Bu	3	5	115	34
4[d]	*t*-Bu	3	10	115	52
5[d]	*t*-Bu	3	15	115	78
6[d]	*t*-Bu	3	20	115	78
7[d]	*t*-Bu	2	15	115	80
8[d]	*t*-Bu	2	15	120	80
9[e]	*t*-Bu	2	15	115	82
10[e]	*n*-Pr	2	15	115	25
11[e]	*n*-Pr	2	20	115	24
12[e]	Me	2	15	115	trace
13[e]	Me	2	20	115	trace

[a]Reaction conditions: **7** (0.5 mol), triethylamine (0.5 mol, 1.0 equiv), acid chloride (0.55 mol, 1.1 equiv), reflux for 3 h. [b]Heat for 3 h. [c]Isolated yield of **9**. [d]Hydrolysis with 1 M hydrochloric acid aqueous. [e]Hydrolysis with H_2O.

not only simplified the operation by avoiding the use of high temperature and strong acid conditions but also reduced the cost by replacing Pd/C with sodium dithionite for reduction of the nitro group. However, this route was tedious (7 steps) and the overall yield was relatively low (29.4%). Moreover, the hypertoxic dimethyl sulfate and dangerous mixed acid were necessary, which greatly increased the safety risks.

Those methods for the synthesis of compound **1** mentioned above suffered from several disadvantages, such as the use of expensive and commercially unavailable raw materials, harsh reaction conditions, dangerous or hypertoxic reagents, and serious environmental pollution, which limited their application in industry. Thus, the development of an efficient, practical, and eco-friendly synthetic route to compound **1** is still highly desirable. Herein, we report an improved, six-step procedure for the synthesis of **1** by starting with commercially available *o*-methylaniline **7**, which afforded compound **1** with 99.91% purity and 51.5% overall yield (Scheme 2). This approach featured simple operation and low production costs and would be suitable for industrial production.

2. RESULTS AND DISCUSSION

2.1. Preparation of *N*-(4-Formyl-2-methylphenyl) Pivalamide 9c. Initially, a series of protecting groups on the *o*-methylaniline **7** were evaluated to secure a selective formylation group at the para position of the amido in **8** for the subsequent reaction.[8]

https://doi.org/10.1021/acs.oprd.1c00025
Org. Process Res. Dev. 2021, 25, 1022−1027

For the introduction of the formyl group on the benzene ring of **8**, the currently common methods include Blanc chloromethylation[9] followed by oxidation,[10] Duff reaction,[11] and Vilsmeier reactions.[12]

Because of the simplicity and easy operation, the Duff reaction was used for the direct formylation of compound **8**. Next, the reaction conditions were investigated (Table 1). It should be noted that the temperature had a nonnegligible impact on the yield. When the temperature was 75 °C, no reaction occurred. Increasing the temperature to 110 °C led to *N*-(4-formyl-2-methylphenyl) pivalamide **9c** in 30% yield with a large amount **8c** remaining. However, further increasing the temperature did not improve the yield obviously (34%) (entries 1−3). Given the importance of acid in the Duff reaction, the amount of trifluoroacetic acid was then optimized. When 10 equiv of trifluoroacetic acid were employed, the formylation of **8c** with methenamine (3 equiv) at 115 °C provided **9c** in 52% yield (entry 4). Increasing the amount of trifluoroacetic acid to 15 equiv improved the yield remarkably (78%) (entry 5). Increased yield was not observed when using 20 equiv of trifluoroacetic acid (entry 6). Notably, there was no significant impact on the yield of **9c** when decreasing the amount of methenamine to 2 equiv (entries 5 and 7). As known, the iminium intermediate of the Duff reaction was hydrolyzed to afford the formylation product. Therefore, the hydrolysis conditions were then screened. It was found that the effect of H_2O was better than hydrochloric acid solution (1 M) during the hydrolysis (entries 7 and 9). Moreover, using toluene instead of ethyl acetate or 1,2-dichloroethane as extraction solvent gained product **9c** with fewer impurities.

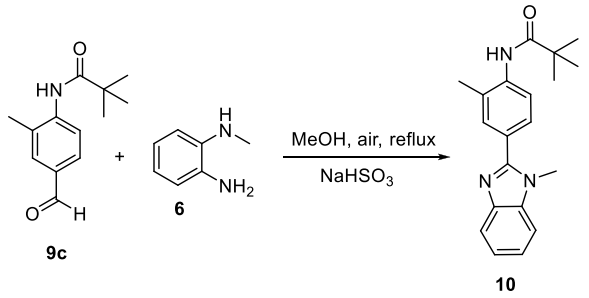
Further research showed that different amino protecting groups greatly influenced the yield of formylation. When using pivaloyl, the formylation yield was 82%, while the yield of *n*-butyryl was only 25%, and the yield of acetyl was trace (entries 9−10 and 12).

Finally, pivaloyl was used as the stable protecting group; optimized reaction conditions for the Duff reaciton were obtained as follows: in the presence of 2.0 equiv of methenamine and 15.0 equiv of trifluoroacetic acid, a mixture reacted at 115−120 °C for 3 h to afford the iminium intermediate, and then the reaction was added with water, stirred for 2 h at 90−95 °C, and extracted with toluene to obtain product **9c** in 82% yield.

2.2. Preparation of *N*-(2-Methyl-4-(1-methyl-1*H*-benzimidazol-2-yl) phenyl) Pivalamide 10. Oxidative condensation is an important method for the synthesis of benzimidazole compounds. Currently common oxidants include H_2O_2,[7] DDQ,[13] $NaHSO_3$,[14] $Fe(ClO_4)_3$,[15] and air.[16] Due to the greenness, atom economy, and sustainability, the traditional metal-free cyclocondensation of **9c** in the presence of air was explored. Air was used as an oxidant to convert most of the raw materials into products, and then $NaHSO_3$ was added to promote the reaction of the remaining substances and shorten the reaction time (Table 2, entries 3, 5−6). The more optimal reaction conditions about the amount of *N*-methyl *o*-phenylenediamine **6** were shown in Table 2.

Briefly, compound **6**, MeOH, and compound **9c** were added and refluxed for 3 h with air, then saturated $NaHSO_3$ was added to speed up the reaction after cooling down. After the completion of the reaction, the mixture was filtrated and washed with MeOH, evaporated to obtain the crude product,

Table 2. Optimization of the Cyclization Reaction[a]



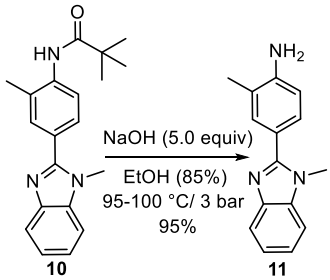
entry	**6** (equiv)	$NaHSO_3$ (equiv)	time (h)	yield (%)[b]
1[c]	1.0	1.5	3	74
2[c]	1.1	1.5	3	80
3[c]	1.2	1.5	3	85
4[c]	1.3	1.5	3	85
5[c]	1.2	2.0	4	84
6	1.2	0	6	72
7[d]	1.2	1.5	3	75
8[d]	1.2	3.0	3	83

[a]Reaction conditions: **9c** (1 equiv, 0.20 mol). [b]Isolated yield of **10**. [c]At the end of the reaction, the mixture was added with saturated $NaHSO_3$ and stirred for 0.5 h. [d]At the beginning of the reaction, the mixture was added with saturated $NaHSO_3$.

and then recrystallized with 45% EtOH in H_2O to obtain the compound **10** in 85% yield.

2.3. Preparation of 2-Methyl-4-(1-methyl-1*H*-benzimidazol-2-yl) Aniline 11. The amide could be hydrolyzed[17] by heating to 170 °C for 7 h with ethylene glycol as solvent and KOH as the base. In order to avoid high temperature conditions and ethylene glycol as solvent, the mixture of 85% EtOH in H_2O was used as green solvent,[18] and the hydrolysis of **10** using NaOH as base under 3 bar pressure conditions at 95−100 °C afforded **11** (Scheme 3). After recrystallization with 35% EtOH in H_2O, the compound **11** was obtained in 95% yield (Table S1).

Scheme 3. Synthetic Method for 2-Methyl-4-(1-methyl-1*H*-benzimidazol-2-yl) Aniline 11

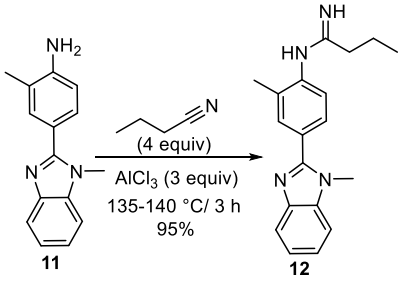


2.4. Preparation of *N*-(2-Methyl-4-(1-methyl-1*H*-benzimidazol-2-yl) phenyl) Butyrimidamide 12. We planned to construct the other benzimidazole ring through Pinner reaction of aniline **11**. The synthesis of **12**[19] via the coupling of **11** with butyronitrile in the presence of Lewis acid was studied. We used cheap $AlCl_3$ as a Lewis acid, when 3 equiv of $AlCl_3$ were employed, and conducting the coupling reaction at 135−140 °C provided crude productof **12** (Scheme 4) in 95% yield (Table S2).

2.5. Preparation of 1,7′-Dimethyl-2′-propyl-2,5′-bi-(1*H*-benzimidazole) 1. For C−N bond coupling to construct

https://doi.org/10.1021/acs.oprd.1c00025
Org. Process Res. Dev. 2021, 25, 1022−1027

Scheme 4. Synthetic Method for *N*-(2-Methyl-4-(1-methyl-1*H*-benzimidazol-2-yl) phenyl) Butyrimidamide 12



a benzimidazole ring, hypervalent iodine(III),[20] $Cu(OAc)_2$,[21] $Zn(OTf)_2$,[22] and NaClO[23] were commonly used. We chose cheap and easily available $Ca(ClO)_2$ as the oxidant, which was beneficial to industrial production. The optimal reaction conditions about the amount of $Ca(ClO)_2$ and NaOH were shown in Table 3. After the optimization, $Ca(ClO)_2$ solution (0.2 M) was slowly added to the reaction mixture (***Caution:*** this was an exothermic reaction, and the $Ca(ClO)_2$ solution needed to be added slowly), until the raw materials reacted fully. Then NaOH solution was added, and the mixture was stirred at 15−20 °C until the intermediate **13** disappeared. The mixture was filtered and washed with MeOH, evaporated to obtain the crude product, and then recrystallized with 50% EtOH in H_2O to obtain target product **1** in 82% yield.

3. CONCLUSION

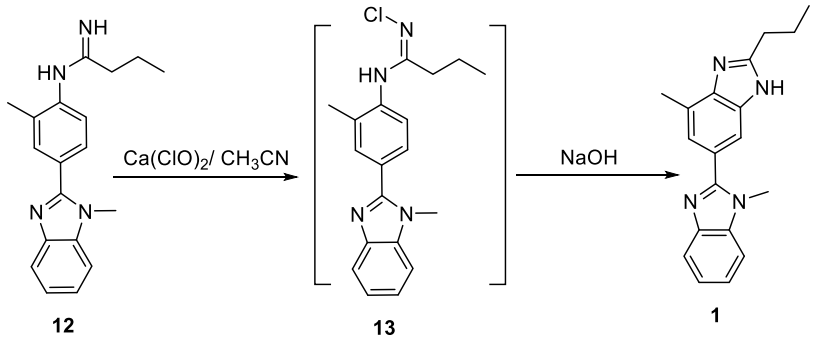
In summary, we developed an improved and practical method for the highly efficient preparation of 1,7′-dimethyl-2′-propyl-2,5′-bi(1*H*-benzimidazole) **1**, a key intermediate for the synthesis of antihypertensive drug telmisartan. The target compound **1** was produced in 51.5% overall yield with a purity of 99.91% by using *o*-methyl aniline as starting material after a six-step process. The merits of the present process were based in the inexpensive and readily available raw material, efficient and selective direct formylation of **8c**, and construction of the bis-benzimidazole by air-mediated oxidative condensation of **9c** with **6** and $Ca(ClO)_2$-promoted direct intramolecular C−N coupling of amidine **12**. Due to the simple operation, cost reduction, and environmental sustainability, the protocol would be suitable for industrial production.

4. EXPERIMENTAL SECTION

4.1. Materials and Methods. All solvents and reagents were purchased from commercial sources and used without further purification unless otherwise indicated. The reactions were monitored by analytical thin-layer chromatography and visualized under UV light (254 and 365 nm). Melting points (mps) were determined on a WRS-2 microcomputer melting point apparatus and were uncorrected. ^1H and ^{13}C NMR were recorded at 400 and 600 MHz, respectively. The chemical shifts are reported as δ ppm using TMS as the internal standard. Mass spectra were measured with a high-resolution MS instrument using ESI ionization.

4.2. Synthesis of *N*-(4-Formyl-2-methylphenyl) Pivalamide (9c). *O*-Methylaniline **7** (324.73 g, 3.0 mol), triethylamine (306.64 g, 3.0 mol), and DCM (2.0 L) were added to a 5 L flask, and the mixture was mechanically stirred for 2 h in an ice−water bath. Pivaloyl chloride was slowly added (401.93 g, 3.3 mol) at 5−10 °C. Then the solution was mechanically stirred at reflux for 3 h. After cooling to room temperature, H_2O (700 mL) and concentrated hydrochloric acid (60.84 g, 0.6 mol) were added slowly. Then, the mixture was stirred for an additional 2 h at 20−25 °C. The organic layer was separated, and the water layer was extracted with DCM (3 × 500 mL). The combined organic fraction was washed with water, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure to the crude product of *N*-(*o*-tolyl) pivalamide **8c** as a white solid (573.01 g, 99.95%). Then, *N*-(*o*-tolyl) trimethylacetamide **8c** (573.01 g, 3.0 mol) and trifluoroacetic acid (5.18 kg, 45 mol) were added to a 30 L flask, and the mixture was mechanically stirred for 1 h at room temperature. Methenamine (849.60 g, 6.0 mol) was added slowly at 40−50 °C, then heated to 115−120 °C in oil bath, and stirred for 3 h. Then the mixture was added with water (15.0 L) and stirred for 2 h at 90−95 °C. The resulting mixture was cooled to room temperature, and toluene (6.0 L) and the mixture were stirred for 0.5 h. The organic layer was separated,

Table 3. Optimization of the Oxidation Reaction[a]



entry	NaOH (equiv)	$Ca(ClO)_2$ (equiv)	temp (°C)	time (h)	yield (%)[b]
1	5	0.8	30−35	2	74
2	5	1.0	30−35	2	78
3	4	1.0	30−35	2	79
4	3	1.0	30−35	2	79
5	3	1.0	15−20	2	82

[a]Reaction conditions: **12** (1.0 equiv, 0.20 mol), CH_3CN (500 mL). [b]Isolated yield of **1**.

https://doi.org/10.1021/acs.oprd.1c00025
Org. Process Res. Dev. 2021, 25, 1022−1027

and the water layer was extracted with toluene (2 × 3.0 L). The acid water layer was distilled to recycle trifluoroacetic acid under reduced pressure. The combined organic layer was washed with 0.45 M Na_2CO_3 solution to adjust the water phase to pH = 7.0−8.0, then dried with anhydrous $MgSO_4$, and concentrated under reduced pressure to obtain the crude product of *N*-(4-formyl-2-methylphenyl) pivalamide **9c** as a white solid (538.74 g, 82%). Mp 46.3−48.6 °C. Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 8.35 (d, J = 8.4 Hz, 1H), 7.73 (dd, J = 10.4, 3.2 Hz, 2H), 7.49 (br s, 1H), 2.34 (s, 3H), 1.35 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.43, 176.71, 141.92, 132.25, 131.17, 129.99, 127.27, 120.98, 40.31, 27.72, 17.57. MS-ESI: m/z 242.1 $[M + Na]^+$, 220.1 $[M + H]^+$.

4.3. Synthesis of *N*-(2-Methyl-4-(1-methyl-1*H*-benzimidazol-2-yl) phenyl) Pivalamide (10). *N*-Methyl-*o*-phenylenediamine **6** (296.17 g, 2.40 mol) and MeOH (2.0 L) were added to a 5 L flask, and the mixture was mechanically stirred for 0.5 h under the room temperature. *N*-(4-Formyl-2-methylphenyl) trimethylacetamide **9c** solid (438.56 g, 2.0 mol) was added to the mixture, which was then refluxed for 3 h. The mixture was cooled at 30−40 °C, and saturated $NaHSO_3$ solution (315.30 g, 3.0 mol) was added, followed by stirring for 1 h. The resulting mixture was filtered, washed with MeOH, and concentrated under reduced pressure to recover the solvent. The crude product was purified by recrystallization with 45% EtOH in H_2O to afford pure *N*-(2-methyl-4-(1-methyl-1*H*-benzimidazol-2-yl)phenyl) pivalamide **10** as a white solid (546.04 g, 85%). Mp 175.4−176.1 °C. Spectral data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 (brs, 1H), 7.73 (d, J = 1.2 Hz, 1H), 7.67−7.64 (m, 2H), 7.61 (d, J = 7.8 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.27 (m, 2H), 3.89 (s, 3H), 2.28 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.75, 153.58, 143.00, 137.53, 136.72, 131.76, 128.61, 127.73, 126.21, 122.78, 122.50, 122.07, 119.77, 109.69, 40.07, 31.84, 27.81, 17.69. MS-ESI: m/z 322.2 $[M + H]^+$.

4.4. Synthesis of 2-Methyl-4-(1-methyl-1*H*-benzimidazol-2-yl) Aniline (11). *N*-(2-Methyl-4-(1-methyl-1*H*-benzimidazol-2-yl)phenyl)pivalamide **10** (513.92 g, 1.6 mol), NaOH (323.23 g, 8.0 mol) and 85% EtOH in H_2O (1.2 L) were added to a 2.5 L flask, and the mixture was mechanically stirred for 1.0 h at 50 °C, then heated to 95 °C with 3 bar of pressure, and stirred for 8 h. The mixture was cooled to room temperature and then evaporated to obtain the crude product. The crude product was purified by recrystallization with 35% EtOH in H_2O to afford pure 2-methyl-4-(1-methyl-1*H*-benzimidazol-2-yl) aniline **11** as a gray solid, (360.39 g, 95%). Mp 147.4−149.9 °C. Spectral data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59−7.57 (m, 1H), 7.53−7.51 (m, 1H), 7.46 (s, 1H), 7.41 (dd, J = 8.4, 1.6 Hz, 1H), 7.24−7.15 (m, 2H), 6.73 (d, J = 8.4 Hz, 1H), 5.36 (brs, 2H), 3.84 (s, 3H), 2.14 (s, 3H). MS-ESI: m/z 238.1 $[M + H]^+$.

4.5. Synthesis of *N*-(2-Methyl-4-(1-methyl-1*H*-benzimidazol-2-yl)phenyl) Butyrimidamide (12). 2-Methyl-4-(1-methyl-1*H*-benzimidazol-2-yl) aniline **11** (355.65 g, 1.5 mol) and butyronitrile (418.50 g, 6.0 mol) were added to a 5 L flask, and the mixture was mechanically stirred for 1.0 h at room temperature. The mixture was added with $AlCl_3$ (606.15 g, 4.5 mol) at 135−140 °C for 3 h. The mixture was cooled at 85 °C, and DCE (1.5 L) was added, followed by cooling to 0−5 °C. Then slow addition of 5 M NaOH ice water solution (742.20 g, 18.0 mol) occurred, with mechanical stirring for 1.0 h. The organic layer was separated, and the water layer was extracted with DCE (2 × 800 mL). The combined organic layer was washed with water to adjust the water phase to pH = 7.0−8.0, then dried with anhydrous $MgSO_4$, and concentrated under reduced pressure to obtain the crude product of *N*-(2-methyl-4-(1-methyl-1*H*-benzimidazol-2-yl) phenyl) butyrimidamide **12** as a brown gray solid (436.30 g, 95%). Mp 131.0−135.5 °C. Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.76 (m, 1H), 7.64 (s, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.40−7.38 (m, 1H), 7.31−7.29 (m, 2H), 6.92 (d, J = 8.0 Hz, 1H), 4.39 (brs, 2H), 3.88 (s, 3H), 2.35 (m, 2H), 2.22 (s, 3H), 1.80−1.79 (m, 2H), 1.08(m, 3H). MS-ESI: m/z 307.2$[M + H]^+$.

4.6. Synthesis of 1,7′-Dimethyl-2′-propyl-2,5′-bi(1*H*-benzimidazole) (1). *N*-(2-Methyl-4-(1-methyl-1*H*-benzimidazol-2-yl)phenyl) butyrimidamide **12** (398.06 g, 1.3 mol) and CH_3CN (3.5 L) were added to a 15 L flask, and the mixture was mechanically stirred for 0.5 h at 5−10 °C. To the mixture was added a solution of 0.2 M $Ca(ClO)_2$ (187.98 g, 1.3 mol) at 10−15 °C, until the raw materials reacted fully. Then a solution of 5 M NaOH (160.68 g, 3.9 mol) was added, with reaction at 15−20 °C for 1 h until the intermediate **13** reacted completely. The reaction was filtered, washed with MeOH, and concentrated under reduced pressure to recover the solvent. The crude product was purified by recrystallization with 50% EtOH in H_2O to afford pure 1,7′-dimethyl-2′-propyl-2,5′-bi(1*H*-benzimidazole) **1** as a white solid (324.27 g, 82%). Purity 99.91% (HPLC). Mp 137.5−139.1 °C. Spectral data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (s, 1H), 7.74 (s, 1H), 7.65 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.42 (s, 1H), 7.25 (m, 2H), 3.89 (s, 3H), 2.84 (d, J = 7.5 Hz, 2H), 2.58 (s, 3H), 1.83 (q, J = 7.4 Hz, 2H), 1.03−0.92 (t, J = 7.4 Hz, 3H). MS-ESI: m/z 305.2 $[M + H]^+$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.1c00025.

Optimization study of the hydrolysis reaction, optimization study of the amidation reaction, HPLC spectra of compound **1**, and NMR, MS data for compounds **9c**, **10**, **11**, **12**, and **1** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Jianhong Zhao − *Engineering Research Center of Pharmaceutical Process Chemistry, Ministry of Education, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China;* orcid.org/0000-0003-1931-5363; Email: zjhpharm@ecust.edu.cn

Authors

Yicheng Xiong − *Engineering Research Center of Pharmaceutical Process Chemistry, Ministry of Education, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China*

Wu-Lin Yang − *Engineering Research Center of Pharmaceutical Process Chemistry, Ministry of Education, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China;* orcid.org/0000-0001-7985-5017

Fan Yang − *Engineering Research Center of Pharmaceutical Process Chemistry, Ministry of Education, School of*

https://doi.org/10.1021/acs.oprd.1c00025
Org. Process Res. Dev. 2021, 25, 1022−1027

Pharmacy, East China University of Science and Technology, Shanghai 200237, China

Yu Jin − *Engineering Research Center of Pharmaceutical Process Chemistry, Ministry of Education, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.oprd.1c00025

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Jiangsu Zhongbang Pharmaceutical Co. Ltd.

■ REFERENCES

(1) Frampton, J. E. Telmisartan: a review of its use in cardiovascular disease prevention. *Drugs* **2011**, *71*, 651−677.

(2) Unger, T. Preclinical and Clinical Effects of RAS Inhibition with a Focus on Telmisartan. *ISRN Vasc. Med.* **2012**, *2012*, 1−11.

(3) Benson, S. C.; Pershadsingh, H. A.; Ho, C. I.; Chittiboyina, A.; Desai, P.; Pravenec, M.; Qi, N.; Wang, J.; Avery, M. A.; Kurtz, T. W. Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARgamma-modulating activity. *Hypertension* **2004**, *43*, 993−1002.

(4) Kumar, A. S.; Ghosh, S.; Soundararajan, R.; Mehta, G. N. An improved synthesis of Telmisartan: an antihypertensive drug. *ARKIVOC* **2009**, *2009*, 247−254.

(5) Ries, U. J.; Mihm, G.; Narr, B.; Hasselbach, K. M.; Wittneben, H.; Entzeroth, M.; van Meel, J. C.; Wienen, W.; Hauel, N. H. 6-Substituted benzimidazoles as new nonpeptide angiotensin II receptor antagonists: synthesis, biological activity, and structure-activity relationships. *J. Med. Chem.* **1993**, *36*, 4040−4051.

(6) Reddy, K. S.; Srinivasan, N.; Reddy, C. R.; Kolla, N.; Anjaneyulu, Y.; Venkatraman, S.; Bhattacharya, A.; Mathad, V. T. An Efficient and Impurity-Free Process for Telmisartan: An Antihypertensive Drug. *Org. Process Res. Dev.* **2007**, *11*, 81−85.

(7) Wang, P.; Zheng, G.-J.; Wang, Y.-P.; Wang, X.-J.; Wei, H.-G.; Xiang, W.-S. Highly practical and cost-efficient synthesis of telmisartan: an antihypertensive drug. *Tetrahedron* **2012**, *68*, 2509−2512.

(8) Wang, G.-B.; Wang, L.-F.; Li, C.-Z.; Sun, J.; Zhou, G.-M.; Yang, D.-C. A facile and efficient method for the selective deacylation of *N*-arylacetamides and 2-chloro-*N*-arylacetamides catalyzed by $SOCl_2$. *Res. Chem. Intermed.* **2012**, *38*, 77−89.

(9) Hu, Y. L.; Lu, M.; Ge, Q.; Wang, P. C.; Zhang, S. B.; Lu, T. T. An inexpensive and convenient procedure for chloromethylation of aromatic hydrocarbons by phase transfer catalysis in aqueous media. *J. Chil. Chem. Soc.* **2010**, *55*, 97−103.

(10) (a) Faisal, M.; Ahmed, M.; Hussain, S.; Larik, F. A.; Saeed, A. Investigating the effectiveness of classical and eco-friendly approaches for synthesis of dialdehydes from organic dihalides. *Green Process. Synth.* **2019**, *8*, 635−648. (b) Faisal, M.; Hussain, S.; Haider, A.; Saeed, A.; Larik, F. A. Assessing the effectiveness of oxidative approaches for the synthesis of aldehydes and ketones from oxidation of iodomethyl group. *Chem. Pap.* **2019**, *73*, 1053−1067. (c) Coman, F.-M.; Mbaveng, A. T.; Leonte, D.; Bencze, L. C.; Vlase, L.; Imre, S.; Kuete, V.; Efferth, T.; Zaharia, V. Heterocycles 44. Synthesis, characterization and anticancer activity of new thiazole ortho-hydroxychalcones. *Med. Chem. Res.* **2018**, *27*, 1396−1407.

(11) (a) Meisner, Q. J.; Younes, A. H.; Yuan, Z.; Sreenath, K.; Hurley, J. J. M.; Zhu, L. Excitation-Dependent Multiple Fluorescence of a Substituted 2-(2′-Hydroxyphenyl)benzoxazole. *J. Phys. Chem. A* **2018**, *122*, 9209−9223. (b) Grimblat, N.; Sarotti, A. M.; Kaufman, T. S.; Simonetti, S. O. A theoretical study of the Duff reaction: insights into its selectivity. *Org. Biomol. Chem.* **2016**, *14*, 10496−10501. (c) Chavan, S. P.; Lasonkar, P. B. One-pot migration-formylation of benzyl aryl ethers under Duff reaction condition. *Tetrahedron Lett.* **2013**, *54*, 4789−4792. (d) Grajda, M.; Wierzbicki, M.; Cmoch, P.; Szumna, A. Inherently chiral iminoresorcinarenes through regioselective unidirectional tautomerization. *J. Org. Chem.* **2013**, *78*, 11597−11601.

(12) Warashina, T.; Matsuura, D.; Sengoku, T.; Takahashi, M.; Yoda, H.; Kimura, Y. Regioselective Formylation of Pyrrole-2-Carboxylate: Crystalline Vilsmeier Reagent vs Dichloromethyl Alkyl Ether. *Org. Process Res. Dev.* **2019**, *23*, 614−618.

(13) Lee, K. J.; Janda, K. D. Traceless solid-phase synthesis of 5-benzoylbenzimidazoles. *Can. J. Chem.* **2001**, *79*, 1556−1561.

(14) Weidner-Wells, M. A.; Ohemeng, K. A.; Nguyen, V. N.; Fraga-Spano, S.; Macielag, M. J.; Werblood, H. M.; Foleno, B. D.; Webb, G. C.; Barrett, J. F.; Hlasta, D. J. Amidino benzimidazole inhibitors of bacterial two-component systems. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1545−1548.

(15) Oskooie, H. A.; Heravi, M. M.; Sadnia, A.; Behbahani, F. K.; Jannati, F. Solventless synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles catalyzed by $Fe(ClO_4)_3$ at room temperature. *Chin. Chem. Lett.* **2007**, *18*, 1357−1360.

(16) Lin, S.; Yang, L. A simple and efficient procedure for the synthesis of benzimidazoles using air as the oxidant. *Tetrahedron Lett.* **2005**, *46*, 4315−4319.

(17) Shimada, I.; Maeno, K.; Kazuta, K.; Kubota, H.; Kimizuka, T.; Kimura, Y.; Hatanaka, K.; Naitou, Y.; Wanibuchi, F.; Sakamoto, S.; Tsukamoto, S. Synthesis and structure-activity relationships of a series of substituted 2-(1*H*-furo[2,3-g]indazol-1-yl)ethylamine derivatives as 5-HT_{2C} receptor agonists. *Bioorg. Med. Chem.* **2008**, *16*, 1966−1982.

(18) Zhu, L. Z.; Sheng, X. H.; Li, Y.; Lu, D.; Qiu, R. H.; Kambe, N. Nickel-Catalyzed Remote C4-H Arylation of 8-Aminoquinolines. *Org. Lett.* **2019**, *21*, 6785−6789.

(19) (a) Digwal, C. S.; Yadav, U.; Ramya, P. V. S.; Sana, S.; Swain, B.; Kamal, A. Vanadium-Catalyzed Oxidative C(CO)-C(CO) Bond Cleavage for C-N Bond Formation: One-Pot Domino Transformation of 1,2-Diketones and Amidines into Imides and Amides. *J. Org. Chem.* **2017**, *82*, 7332−7345. (b) Song, L. N.; Tian, X. H.; Lv, Z. G.; Li, E. T.; Wu, J.; Liu, Y. X.; Yu, W. Q.; Chang, J. B. I_2/KI-Mediated Oxidative N-N Bond Formation for the Synthesis of 1,5-Fused 1,2,4-Triazoles from *N*-Aryl Amidines. *J. Org. Chem.* **2015**, *80*, 7219−7225.

(20) Reddy Kandimalla, S.; Prathima Parvathaneni, S.; Sabitha, G.; Subba Reddy, B. V. Recent Advances in Intramolecular Metal-Free Oxidative C-H Bond Aminations Using Hypervalent Iodine(III) Reagents. *Eur. J. Med. Chem.* **2019**, *2019*, 1687−1714.

(21) Brasche, G.; Buchwald, S. L. C-H functionalization/C-N bond formation: copper-catalyzed synthesis of benzimidazoles from amidines. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932−1934.

(22) Zhu, Z. Z.; Cen, J. H.; Tang, X. D.; Li, J. X.; Wu, W. Q.; Jiang, H. F. Access to Amidines and Arylbenzimidazoles: Zinc-Promoted Rearrangement of Oxime Acetates. *Adv. Synth. Catal.* **2018**, *360*, 2020−2031.

(23) Hisano, T.; Ichikawa, M.; Tsumoto, K.; Tasaki, M. Synthesis of Benzoxazoles, Benzothiazoles and Benzimidazoles and Evaluation of Their Antifungal, Insecticidal and Herbicidal Activities. *Chem. Pharm. Bull.* **1982**, *30*, 2996−3004.