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Synthesis of Imatinib by C−N Coupling Reaction of Primary Amide and Bromo-Substituted Pyrimidine Amine

Cuiling Wang,*[,†] Xiao Bai,[†] Rui Wang,[†] Xudong Zheng,[†] Xiumei Ma,[†] Huan Chen,[†] Yun Ai,[†,‡] Yajun Bai,[§] and Yifeng Liu[∥]

[†]College of Life Sciences, Northwest University, Xi'an 710069, China
[‡]Xi'an Institute for Food and Drug Control, Xi'an 710054, China
[§]Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of the Ministry of Education, College of Chemistry & Materials Science, Northwest University, Xi'an 710127, China
[∥]Applied Chemical Institute, Northwest University, Xi'an 710069, China

Supporting Information

ABSTRACT: A new method for imatinib synthesis is described by using the C−N coupling reaction of 4-(4-methylpiperazine-1-methyl)benzamide with *N*-(5-bromo-2-tolyl)-4-(3-pyridyl)pyrimidin-2-amine to form imatinib. In this synthetic route, the high efficiency and high selectivity of nano-ZnO as a catalyst is key to the mild hydrolysis of 4-(4-methylpiperazine-1-methyl)benzonitrile into the corresponding amide. The total imatinib yield was 51.3%, and the purity was 99.9%. This simple and effective synthetic pathway avoids gene-impurity production (as classified by the FDA Center for Drug Evaluation and Research), and the synthesis is environmentally friendly with a short reaction time.

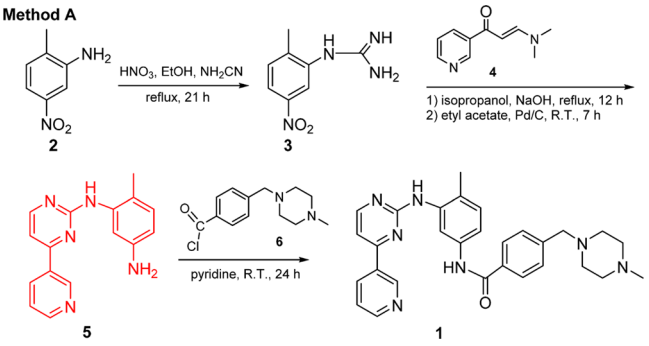
KEYWORDS: *imatinib, nano-ZnO, C−N coupling reaction, bromopyrimidine, piperazine amide*

INTRODUCTION

Imatinib mesylate is a synthetic tyrosine kinase inhibitor, which is used widely in the clinical treatment of chronic myeloid leukemia.[1,2] Chronic myeloid leukemia is an acquired myeloproliferative disorder that is characterized by cytogenetic translocation, which forms a fusion kinase BCR-Abl.[3,4] Imatinib(4-[(4-methyl-1-piperazinyl)methyl]-*N*-[4-methyl-3-[[4-(3-pyridyl)-2-pyrimidinyl] amino]-phenyl]benzamide)) (**1**) is the first specific molecular targeting drug inhibitor of BCR-Abl fusion protein and a first-line therapeutic drug for this type of case.[5,6] In recent years, its applications have gradually expanded to the treatment of diffuse cutaneous mastocytosis and benign prostatic hyperplasia.[7]

Because it is a well-established gold-standard drug in the treatment of chronic myeloid leukemia, many methods have been developed for the synthesis of imatinib.[8−10] The synthetic route was first proposed by Zimmermann (Ciba−Geigy).[8] The Zimmermann route (Method A in Scheme 1) is the most mainstream synthetic route, and it mainly converts aniline (**2**) to a guanido-containing compound (**3**), which is then reduced to a pyrimidine amine (**5**) by a two-step hydrazine and enone amine (**4**) treatment. Compound **5** reacts with an acyl chloride (**6**) to form imatinib (**1**). In 2008, we proposed a synthetic imatinib method (Method B in Scheme 2),[10a] which uses a new starting material, 2-bromo-4-nitrotoluene (**7**), and the copper-catalyzed C−N coupling reaction, followed by a reduction of the nitro group to compound **5** by the $N_2H_4{\cdot}H_2O/FeCl_3/C$ system, and finally the target compound (**1**) is produced. This improved method for imatinib preparation is less hazardous and more environmentally friendly and has potential for industrial application.

Scheme 1. Zimmermann's Method of Synthesis of Imatinib



However, additional problems have surfaced in recent years with the increase in clinical cases of imatinib. The genotoxic impurities in imatinib drugs have raised much attention. Two impurities in imatinib mesylate, namely, *N*-(5-amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyridineamine (**5**) and 4-chloromethyl-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-yl-amino)-phenyl]benzamide (**10**), have been reported by the FDA's Center for Drug Evaluation and Research. The impurities in imatinib mesylate have the potential for direct DNA damage and toxicity to genes, with genotoxic impurity limits of below 20 (**5**) and 10 ppm (**10**), respectively. In previous reports, these two substances were found mostly as intermediates (Schemes 1 and 2). Purification to remove two genotoxic impurities is difficult. The most effective way to

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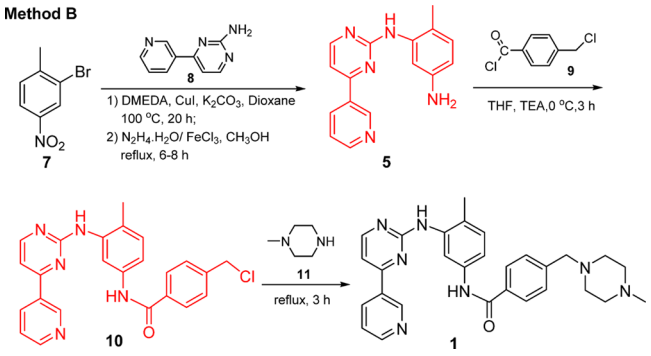
Scheme 2. Our Previous Imatinib Synthetic Route



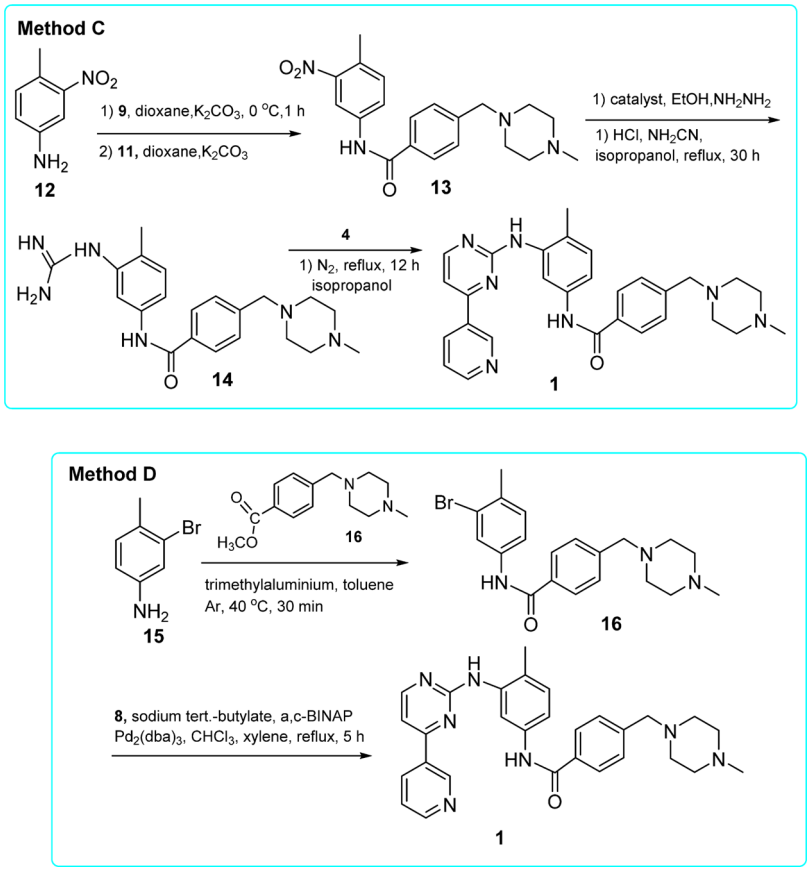
resolve this problem is to modify the synthetic route and to avoid the production of these genotoxic impurities.

In fact, in 2003, Zimmermann's inverse synthesis route was designed by Loiseleur et al. (Methods C and D in Scheme 3).[9] Method C consists of 3-nitro-4-methyl aniline (**12**) as the starting material with the first acylation; then, the pyrimidine ring was built. Method D uses 3-bromo-4-methylaniline (**15**) as the starting material and the C−N coupling reaction to build phenylaminopyrimidine, in combination with two precious catalysts: tris(dibenzylideneacetone)dipalladium (Pd2(dba)3) and organophosphorus ligand (±)-2,2′-bis-(diphenylphosphine)-1,1′-binaphthyl (rac-BINAP). Both routes do not produce genotoxic impurities. However, these methods have some shortcomings, such as the poor selectivity of the acylation reaction, high synthesis costs, and long reaction times. Thus the development of an effective method for imatinib synthesis is required that avoids the production of these genotoxic impurities. We designed a new synthetic imatinib route (Scheme 4) by using the C−N coupling reaction of *N*-(5-bromo-2-tolyl)-4-(3-pyridyl) pyrimidin-2-amine (**17**) with 4-(4-methylpiperazine-1-methyl)benzamide (**18**) to synthesize imatinib (**1**). This simple and effective synthetic pathway avoids gene-impurity production (compounds: **5** and **10**), and the synthesis is environmentally friendly with a short reaction time.

RESULTS AND DISCUSSION

According to our designed synthetic route, six steps are required to synthesize imatinib. The synthesis of *N*-(5-bromo-2-tolyl)-4-(3-pyridyl)pyrimidin-2-amine (**17**) and 3-(dimethylamino)-1-(3-pyridyl)-2-propen-1-one (**4**) has been reported in the literature. The latter synthesis requires toluene or xylene as a solvent during the reaction, and the equipment utilization rate is low with a long reaction time. We obtained satisfactory results by using the solvent-free synthesis of 3-(dimethylamino)-1-(3-pyridyl)-2-propen-1-one (**4**). To improve this method, a Vigreux rectification column needs to be installed on the reaction unit. During the reaction, byproduct methanol that was produced by the reaction was fractionated continuously, the enamine (**4**) yield exceeded 95% after 4−6 h. The solid-phase synthesis of 4-(4-methylpiperazine-1-methyl)benzonitrile (**20**) and its hydrolysis to amide (**18**) and the synthesis of imatinib (**1**) by the C−N coupling reaction occurred as follows.

Scheme 3. Loiseleur's Methods for Imatinib Synthesis



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Scheme 4. Newly Designed Synthetic Methods and Pathways for Imatinib

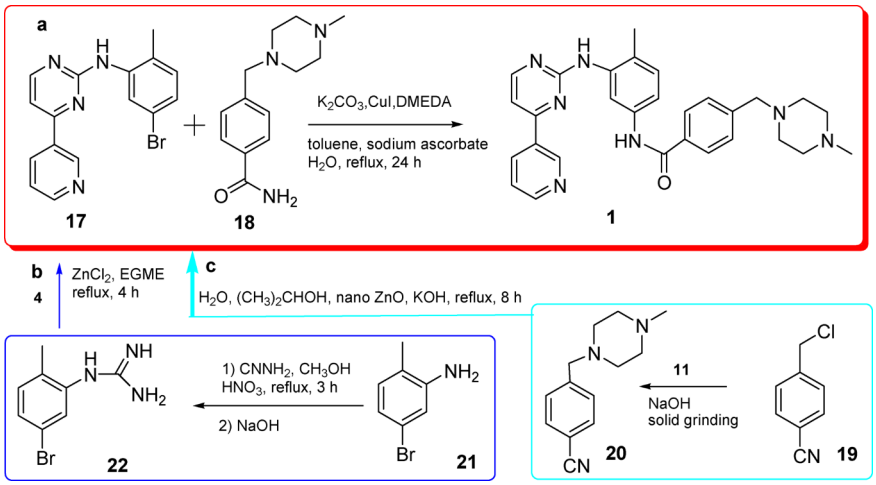
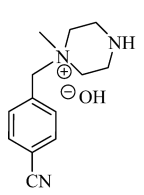


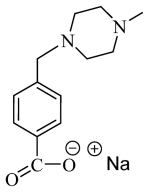
Table 1. Results from the Solid-Phase Synthesis of 4-(4-Methylpiperazine-1-methyl)benzonitrile

no.	piperazine/mol	benzonitrile/mol	NaOH/mol	KOH/mol	H_2O/mL	target products/g	yield/%
1	0.2	0.19	0.2		6	39.1	90.8
2	0.2	0.19	0.2		6	40.2	93.4
3	0.2	0.19	0.2		6	39.6	92.0
4	0.2	0.19		0.2	6	39.3	91.3
5	0.2	0.19		0.2	6	39.1	90.8

Solid-Phase Synthesis of 4-(4-Methylpiperazine-1-methyl)benzonitrile (20). The conventional synthesis of 4-(4-methylpiperazine-1-methyl)benzonitrile (**20**) was achieved by a solvent method. Kompella et al.[11] used chloroform as a solvent to react *N*-methyl piperazine (**11**) with 4-bromomethyl benzonitrile at room temperature for 4 h to obtain 4-(4-methylpiperazine-1-methyl)benzonitrile (**20**). Cheng et al.[12] provided chloroform as a solvent in the presence of sodium carbonate for reaction at 25−30 °C for 12 h to yield 4-(4-methylpiperazine-1-methyl)benzonitrile (**20**). Umezu et al.[13] reported that *N*-methyl piperazine (**11**) was condensed with 4-chloromethyl benzonitrile (**19**) in the presence of sodium carbonate in xylene to form 4-(4-methylpiperazine-1-methyl)-benzonitrile (**20**). These methods have many drawbacks: (a) The use of a large amount of chloroform as a solvent is harmful to the environment and the operator, and chloroform is a solvent that is restricted in technical guidance for the research of residual solvents of chemical drugs. The use of chloroform is highly restricted. (If chloroform is used, then the solvent residue must be controlled below 0.006%.) (b) 4-Bromo-methyl benzonitrile is costly and severely toxic, and 4-chloromethyl benzenitrile (**19**) should be used, which is affordable and easily available. (c) Many byproducts result, and the tertiary amine of *N*-methyl piperazine (**11**) reacts easily with the chloromethyl group to form quaternary ammonium hydroxide (**23**), which easily converts the nitrile group into carboxylate (**24**) when alkali is added. (d) The reaction time is long, and the synthesis efficiency is low.

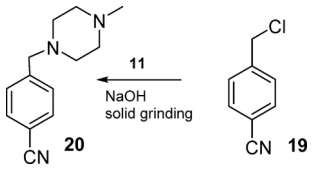


(**23**)



(**24**)

We used solid-phase organic synthesis to obtain 4-(4-methylpiperazine-1-methyl)benzonitrile (**20**) by the solid-phase formation of *N*-methyl piperazine (**11**) and 4-chloromethyl benzonitrile (**19**) in the absence of solvent (Scheme 4c). The reaction formula is as follows (see part of Scheme 4).



Certain amounts of 4-chloromethyl benzonitrile (**19**), *N*-methyl piperazine (**11**), and 50% aqueous sodium hydroxide solution were added to the solid grinding vessel, and after grinding at room temperature for 30 min under cooling, the reaction mixture was placed in the reactor for 0.5 h. 4-(4-Methylpiperazine-1-methyl)benzonitrile (**20**) was obtained by extraction, cooling, crystallization, and filtration with cyclohexane at 70 °C, and its yield exceeded 95%. Under the control of the reaction conditions, almost no side reactions occurred. This method is environmentally friendly, saves time, and produces high yields of target products. Table 1 shows results from the solid-phase synthesis of 4-(4-methylpiperazine-1-methyl)benzonitrile.

The excess of *N*-methyl piperazine (**11**) relative to 4-chloromethyl benzonitrile (**19**) allows for the complete

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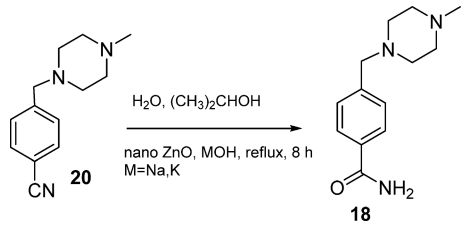
Table 2. Results from the Synthesis of 4-(4-Methylpiperazine-1-methyl)benzamide by Nitrile Hydrolysis

no.	benzonitrile/mol	H_2O/mol	nano-ZnO/mol	KOH/mol	NaOH/mol	benzamide/g	yield/%
1	0.2	0.2	0.01	0.02		43.5	93.1
2	0.2	0.2	0.01	0.02		42.8	91.6
3	0.2	0.2	0.01	0.02		44.0	94.2
4	0.2	0.2		0.02		30.5	65.3
5	0.2	0.2	0.01		0.02	40.5	86.7
6	0.2	0.2	0.01		0.02	39.1	83.7

reaction of 4-chloromethyl benzonitrile (**19**) to avoid difficulties in the removal of unreacted 4-chloromethyl benzonitrile (**19**). When the mole ratio of piperazine (**11**)/benzonitrile (**19**)/NaOH or KOH is 0.2:0.19:0.2 regardless of the base, the yields of 4-(4-methylpiperazine-1-methyl)-benzonitrile (**20**) are higher (90.8, 93.4, 92.0, 91.3, and 90.8%) (Table 1). Because NaOH or KOH must be moisturized by water for its complete participation in the reaction, a minimal amount of water was used to moisturize NaOH or KOH. In this experiment, when 0.2 mol NaOH or KOH was added to the reaction system, 6 mL of water was sufficient to moisturize it. Therefore, the ideal reaction conditions are as follows: The mole ratio of piperazine (11)/benzonitrile (19)/NaOH or KOH is 0.2:0.19:0.2 with a small amount of water, ensuring a smooth reaction. The results also indicate that sodium and potassium hydroxide are ideal raw materials, but sodium hydroxide is cheaper and is more suitable.

Synthesis of 4-(4-Methylpiperazine-1-methyl)-benzamide (18) by Nitrile (20) Hydrolysis. A method to convert 4-(4-methylpiperazine-1-methyl)phenylnitrile (**20**) into 4-(4-methylpiperazine-1-methyl)benzamide (**18**) has not been reported in previous literature, but an increased number of reports exist of similar nitriles being converted to amides. Four main methods exist: (a) Acid and alkali hydrolysis:[14] The classical hydrolysis method uses a strong acid and a strong base as a catalyst, which requires a higher reaction temperature and is prone to excessive hydrolysis and the formation of byproducts. The process yield is low, and the byproduct, carboxylic acid, is not easily removed. (b) Oxidation method: During oxidation, nitrile is converted to amide using hydrogen peroxide as an oxidant. The synthetic pathway for hydrogen peroxide to oxidize nitrile to yield amide was described by McMaster's group in 1916. However, the shortcoming of this approach is that the oxidation reaction has a poor selectivity. In recent years, scientists have tried to improve the reaction results by adding some highly selective catalysts, such as heteropolyacids.[15] (c) Enzymatic catalysis:[16,17] The nitrile is hydrolyzed to the amide by nitrile hydratases. Nitrile hydratases contain two different metal centers, cobalt and iron. Therefore, the addition of Co^{2+} and Fe^{2+} in a bacterial culture has a strong promoting effect on the enzyme activity. This method has the advantage of a high reaction selectivity, mild conditions, and environmental protection. However, it also has the disadvantage of being more responsive and sensitive to the environment. (d) Transition-metal catalytic hydrolysis: This approach is a commonly used method for the hydrolysis of nitriles to amides. The metal ions are mainly Pd, Cu, In, Au, and Ru.[18−20] Ma et al.[21] reported that the aromatic, fatty, and heterocyclic nitriles were smoothly hydrolyzed to the corresponding amide in the presence of acetaldehyde oxime by using $NiCl_2{\cdot}6H_2O$ as a catalyst. However, most methods use precious metals, which increases the reaction cost. Although some methods use inexpensive Cu and Ni, they are supplemented with a large amount of organic compounds, such as acetaldehyde oxime, which makes the reaction system more complicated and the product purification more difficult.

We used a combination of high-efficiency and highly selective catalysts, nano-ZnO (15−25 nm, 99.5% metals basis) and KOH, to mildly hydrolyze 4-(4-methylpiperazine-1-methyl)benzonitrile (**20**) to 4-(4-methylpiperazine-1-methyl)benzoylamide (**18**) (Scheme 4c). The reaction conditions are mild and the selectivity is high, so excessive nitrile hydrolysis is effectively controlled. The reaction formula is as follows (consider part of Scheme 4).



During the reaction, by using isopropanol as the solvent and nano-ZnO, KOH, or NaOH in a catalytic amount and with the addition of a theoretical amount of water (based on the moles of nitrile), 4-(4-methylpiperazine-1-methyl)benzonitrile (**20**) can be hydrolyzed to 4-(4-methylpiperazine-1-methyl)-benzamide (**18**) at the isopropanol reflux temperature. The hydrolysis test results of 4-(4-methylpiperazine-1-methyl)-benzonitrile (**20**) are given in Table 2.

The classical hydrolysis method of nitrile to amide uses a strong acid or a strong base as a catalyst, which is prone to excessive hydrolysis, and the formation of byproducts carboxylic acid is not removed easily. A good yield was obtained by catalyzing the hydrolysis of 4-(4-methylpiperazine-1-methyl)benzonitrile (**20**) with a combination of nano-ZnO and KOH (nano-ZnO (mol)/KOH (mol) 1:2). When the mole ratio of benzonitrile (**20**)/water/nano-ZnO/KOH is 0.2:0.2:0.01:0.02, 4-(4-methylpiperazine-1-methyl)benzamide (**18**) is produced in higher yield (93.1, 91.6, and 94.2%). In contrast, compound (**18**) was generated in lower yield (65.3%) in the absence of nano-ZnO in this reaction system. The synergistic effect of nano-ZnO is very obvious, but the specific reaction mechanism is still unclear. The catalyst with KOH in the hydrolysis has a better yield (>90%) than the NaOH catalysis (∼80% more), which may be related to the alkaline strength.

Synthesis of Imatinib (1) Based on C−N Coupling Reaction. The usual C−N coupling reaction is carried out mostly by using an aromatic amine or other more basic amine and a halogenated aromatic hydrocarbon. In recent years, many reports have been produced on the C−N coupling reaction of amides,[22,23] but because the amide basicity is much weaker than that of the aromatic amine or pyrimidine amine, the yield of the target product that is obtained from the C−N

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Table 3. Results from C−N Coupling Reaction of Pyrimidinyl Amine (17) and Benzamide (18)

no.	pyrimidinyl amine/mol	benzamide/mol	H_2O/mL	*d*-isoascorbate/mol	CuI/mol	K_2CO_3/mol	DMED/mol	imatinib yield/%
1	0.1	0.13	5	0.005	0.02	0.2	0.015	83.5
2	0.1	0.13	5	0.005	0.02	0.2	0.015	82.8
3	0.1	0.13	5	0.005	0.02	0.2	0.015	84.1
4	0.1	0.11	5	0.005	0.02	0.2	0.015	80.0
5	0.1	0.13		0.005	0.02	0.2	0.015	65.4
6	0.1	0.13	5		0.02	0.2	0.015	20.1

coupling reaction with the brominated aromatic hydrocarbon is very low. Previous methods for synthesizing imatinib (Scheme 2, Method B; Scheme 3, Method D) were C−N coupling reactions with pyrimidine amines and brominated aromatic hydrocarbons,[10,24] which proceeded easily, and the yields were high. In our synthetic imatinib route (Scheme 4), 4-(4-methylpiperazine-1-methyl)benzamide (**18**) and *N*-(5-bromo-2-methylphenyl)-4-(3-pyridyl)pyrimidine-2-amine (**17**) reacted according to conventional C−N coupling reaction conditions, and the obtained imatinib yield was low. Therefore, it is noteworthy that an increase in the yield of the C−N coupling reaction of this amide has become a key issue.

After years of research, we finally resolved this problem. We found that water can promote this C−N coupling reaction in a nonpolar solvent. The use of the antioxidant *d*-ascorbate can replace the protection of nitrogen or other inert gases. This simplifies the process equipment and the difficulty of operation. The results of the C−N coupling reaction tests as conducted in accordance with this synthesis method are shown in Table 3.

When the mole ratio of pyrimidinyl amine (**17**)/benzamide (**18**)/*d*-isoascorbate/CuI/K_2CO_3/DMED is 0.1:0.13:0.005:0.02:0.2:0.015, imatinib can be synthesized by a C−N coupling reaction with water (5 mL) with a yield of 83.5, 82.8, and 84.1% (Table 3). We found that water has a significant promoting effect on this C−N coupling reaction in a nonpolar solvent (toluene, xylene). When the solvent was DMF or DMSO, water failed to facilitate the reaction. Imatinib was obtained in a yield of 65.4% in the absence of water in the reaction system (Table 3). The protective effect of the antioxidant *d*-sodium ascorbate on the reaction system is also very obvious. Without the protective effect of antioxidant *d*-sodium ascorbate, the yield of imatinib is only 20.1%. In addition, it is necessary to add excessive 4-(4-methylpiperazine-1-methyl)benzamide (**18**) to the reaction system so that *N*-(5-bromo-2-methylphenyl)-4-(3-pyridyl)pyrimidine-2-amine (**17**) is reacted as completely as possible to facilitate the subsequent imatinib purification. Because the properties of *N*-(5-bromo-2-methylphenyl)-4-(3-pyridyl)pyrimidine-2-amine (**17**) are close to those of imatinib, their separation is difficult. Whereas 4-(4-methylpiperazine-1-methyl)benzamide (**18**) has a certain solubility in hot water, imatinib is completely insoluble in water and can be easily removed from the target product. The elemental analysis of the synthesized imatinib, as well as the IR, MS, and ^{1}H NMR spectral analysis, was consistent with the expected structural characterization data. High-performance liquid chromatography (HPLC) was used to analyze the content, and HPLC-MS was used to detect the genetoxic impurities (compounds **5** and **10**). The content of imatinib that was obtained by our synthetic method was 99.9%, and it did not detect genetic impurities in imatinib from our new method (data provided in the Supporting Information).

Therefore, the new synthetic route of Scheme 4 was used to couple *N*-(5-bromo-2-methylphenyl)-4-(3-pyridyl)pyrimidine-2-amine (**17**) and 4-(4-methylpiperazine-L-methyl)benzamide (**18**) with 2-methyl-5-bromoaniline (**21**) as a raw material through the C−N coupling reaction of amide to produce imatinib (total yield: 51.3%), which did not result in genotoxic impurities restricted by the FDA.

CONCLUSIONS

A new synthetic imatinib route has been developed by the C−N coupling reaction of 4-(4-methylpiperazine-1-methyl)-benzamide (**18**) with *N*-(5-bromo-2-tolyl)-4-(3-pyridyl) pyrimidin-2-amine (**17**). The intermediate, 4-(4-methylpiperazine-1-methyl)benzonitrile (**20**), was obtained by the reaction of *N*-methyl piperazine (**11**) with 4-chloromethyl benzonitrile (**19**) under solvent-free conditions at room temperature with a yield of 93.4%. By using a high-efficiency and selective nano-ZnO catalyst, 4-(4-methylpiperazine-1-methyl)benzonitrile (**20**) was mildly hydrolyzed into the corresponding amide (**18**) with a yield of 94.2%. This synthetic route and process is simple and environmentally friendly and has a short reaction time and good selectivity, and the total yield of imatinib (**1**) was 51.3% (2-methyl-5-bromoaniline (21) as raw material), with a purity of 99.9%. More importantly, the final product imatinib does not contain genotoxic impurities, as reported by the FDA's Center for Drug Evaluation and Research.

EXPERIMENTAL SECTION

General. Melting points were determined on a WRS-1B digital melting-point apparatus (Shanghai YiCe Instrument Equipment) in open capillary tubes and were uncorrected. Elemental analyses were performed by an Elementar Vario EL III instrument. IR spectra were recorded on a Bruker Equinox-55 apparatus. ^{1}H NMR spectra were recorded on a Varian Inova 600 MHz instrument using DMSO-d_6 as a solvent with chemical shifts that were reported relative to tetramethylsilane. The product purity was analyzed by using an Agilent 1100 HPLC with a DAD detector and a Zorbax SB-C_{18} column (250 mm × 4.6 mm, 5 μm), a column temperature of 30 °C, a mobile phase of methanol (0.1% formic acid)-water (50:50), a flow rate of 0.6 mL·min^{-1}, a detection wavelength of 254 nm, and an injection volume of 10 μL. Liquid chromatography (LC-MS) was performed by using an Agilent 1200 HPLC apparatus coupled to an Agilent 6520 quadrupole time-of-flight mass spectrometer (EI). Flash-column chromatography was performed with silica gel (100−200 mesh). An imatinib standard sample was purchased from Sigma-Aldrich Life Science and High Technology. ZnO (15−25 nM, 99.5% metals basis, Aladdin Reagent). All other reagents were used as purchased from commercial suppliers without further purification. All materials were weighed in air.

General Procedure for the Synthesis of Compounds. *3-(Dimethylamino)-1-(3-pyridyl)-2-propen-1-one (4).* Acetyl-

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pyridine (68.6 mL, 0.6 mol) and *N*,*N*-dimethylformamide dimethylacetal (94.7 mL, 0.72 mol) were charged into a reaction flask equipped with a mechanical stirrer and a Vigreux column. The reaction mass was heated slowly with stirring, and the Vigreux column top temperature was controlled at 65 °C. After being maintained for 5 h, the temperature of the reaction mass was gradually heated to 100 °C, and the methanol that was formed in the reaction was distilled off. The reaction mass was cooled to 80 °C, and a mixture of toluene (20 mL) and hexane (10 mL) was added to the reaction mass and stirred for 10 min until the liquid reaction mass and solvents were well mixed. The resultant reaction mass was poured into a beaker and cooled to room temperature. The crystalline solid was filtered off under vacuum and dried at 50−60 °C to yield 3-(dimethylamino)-1-(3-pyridyl)-2-propen-1-one as an orange crystal (101.5 g, yield: 96.0%). Melting point: 81.5−82.2 °C (consistent with the literature).[25]

*5-Bromo-2-methylphenylguanidine (**22**).* 5-Bromo-2-methylaniline (**21**) (37.4 g, 0.2 mol) and methanol (60 mL) were placed in a reactor flask with a mechanical stirrer and a dropping funnel. Nitric acid (65%, 10.8 mL, 0.24 mol) was added dropwise to the reaction mass over 20 min, and the reaction temperature was increased to 60 °C. After stirring for 30 min, a 50% aqueous cyanamide solution (11.7 mL, 0.3 mol) was added dropwise over 40 min. The reaction mixture was heated to the reflux temperature and stirred for 1.5 h; then, 65% nitric acid (7.2 mL 0.16 mol) was added over 20 min. While the reaction mixture was stirred for a further 30 min, 50% aqueous cyanamide solution (7.8 mL, 0.2 mol) was added dropwise over 40 min. The reaction mixture was kept at the reflux temperature for 3 h. After the completion of the reaction, the reaction mass was cooled to room temperature. The solid product was filtered, washed with toluene (20 mL), and dried to yield 5-bromo-2-methylphenylguanidine nitrate as light-brown granular crystals (46.5 g, yield: 79.9%). Melting point: 183−184 °C. 5-Bromo-2-methylphenylguanidine nitrate and distilled water (150 mL) were added to a beaker at room temperature with the addition of 130 mL of 5% NaOH aqueous solution. The reaction mass was stirred for 1 h and filtered to yield a crude product of 5-bromo-2-methylphenylguanidine. The crude product was recrystallized from toluene to give 5-bromo-2-methylphenylguanidine as white powder crystals (34.1 g, yield: 74.8%). Melting point: 76−79 °C. Anal. calcd for $C_8H_{10}BrN_3$: C, 42.13; H, 4.42; N, 18.42. Found: C, 42.51; H, 4.18; N, 18.09. IR (KBr, cm^{-1}): 3452.4, 3376.8, 3139.1, 2963.8, 2758, 1699.3, 1671.9, 1631.5, 1580.2, 1479.7, 1392.8, 882.08, 797.81. ^{1}H NMR (DMSO-d_6, 600 MHz) δ 7.04 (d, 1H), 6.96 (d, 1H), 6.88 (s, 1H), 5.42 (bs, 4H), 2.02 (s, 3H).

*N-(5-Bromo-2-methylphenyl)-4-(3-pyridyl)pyrimidine-2-amine (**17**).* A reaction flask was charged with 5-bromo-2-methylphenylguanidine (**22**) (45.6 g, 0.2 mol), 3-(dimethylamino)-1-(3-pyridyl)-2-propen-1-one (**4**) (38.8 g, 0.22 mol), and ethylene glycol monomethyl ether (EGME) (120 mL). The reaction mixture was heated to reflux (~120 °C) for 8 h, and the reaction mass was cooled to room temperature. The crude product was filtered under reduced pressure, and the precipitate was washed with 20 mL of water on a filter funnel. The product was recrystallized from toluene to yield 55.6 g (81.5%) of *N*-(5-bromo-2-methylphenyl)-4-(pyridin-3-yl)-pyrimidin-2-ylamine (**17**) as a light-yellow powder. Melting point: 152−156 °C. Anal. calcd for $C_{16}H_{13}BrN_4$: C, 56.32; H, 3.84; N, 16.42. Found: C, 56.23; H, 3.86; N, 16.51. MS: 341.0 (M + H), 343.0 (bromine isotope peak), 363.0 (M + Na). IR (KBr, cm^{-1}): 3204.3, 3156.2, 3039.6, 2947, 2892.1, 1581.9, 1533.5, 1454.7, 1421, 1403, 1384, 1337.3, 1294.7, 1024, 990.48, 858.96, 799.05, 710.47, 655, 612.47. ^{1}H NMR (DMSO-d_6, 600 MHz) δ 9.26 (s, 1H, NH), 9.03 (s, 1H), 8.69 (d, 1H), 8.54 (dd, 1H), 8.41 (d, 1H), 7.89 (dd, 1H), 7.54−753 (m, 1H), 7.48 (dd, 1H), 7.22 (d, 1H), 7.19 (d, 1H), 2.22 (s, 3H).

*4-(4-Methylpiperazin-1-ylmethyl)-benzonitrile (**20**).* *N*-Methylpiperazine (22.2 mL, 0.2 mol) and a solution of NaOH (8 g, 0.2 mol) in 6 mL of water were charged into a 90 mm diameter ceramic mortar. The reaction mass was ground constantly in an ice bath until the liquid became semisolid. 4-Chloromethylbenzonitrile (**19**) (28.8 g, 0.19 mol) was gradually added over 30 min, and the temperature of the reaction mass was maintained below room temperature. Thereafter, the reaction mass remained stationary for 2 h before being transferred to a beaker that was charged with 30 mL of cyclohexane. The reaction mixture was heated to 70 °C for 10 min. The cyclohexane layer was poured out and cooled to room temperature. The product was filtered to give 4-(4-methylpiperazin-1-ylmethyl)-benzonitrile (**20**) as white granular crystals (39.1 g, yield: 90.8%). Melting point: 65−68 °C. Anal. calcd for $C_{13}H_{17}N_3$: C, 72.52; H, 7.96; N, 19.52. Found: C, 72.14; H, 7.48; N, 19.01. IR (KBr, cm^{-1}): 3042.6, 2941.8, 2798.5, 2788.9, 2223.8, 1606.6, 1504.5, 1455.7, 1369.1, 1351.4, 1318, 1283.7, 1162.7, 1141.7, 1010.7, 925.3, 855.4, 809.9. ^{1}H NMR (DMSO-d_6, 600 MHz) δ 7.81 (d, 2H), 7.54 (d, 2H,), 3.57 (s, 2H, CH_2), 2.39 (bs, 8H), 2.18 (s, 3H, CH_3).

*4-(4-Methylpiperazin-1-ylmethyl)benzamide (**18**).* A reaction flask was charged with 4-(4-methylpiperazin-1-ylmethyl)-benzonitrile (**20**) (43.1 g, 0.2 mol), isopropyl alcohol (100 mL), water (3.6 mL, 0.2 mol), nano-ZnO (0.81 g, 0.01 mol), and KOH (1.1 g, 0.02 mol). The reaction mixture was heated to reflux for 6−8 h. After a portion of isopropyl alcohol had been distilled off, the mother liquor was filtered by hot filtration to remove the catalyst residue. The reaction mass was poured into a beaker and brought to room temperature for 8 h. The precipitated solid was isolated by filtration and placed into a beaker charged with 100 mL of distilled water. The mixture was heated to 90 °C for 10 min. Hot filtration was carried out, and the mother liquor was brought to room temperature. The solid product was filtered, washed with water, and dried to yield 4-(4-methylpiperazin-1-ylmethyl)benzamide (**18**) as white granular crystals (43.5 g, yield: 93.1%). Melting point: 156−159 °C. Anal. calcd for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01. Found: C, 66.31; H, 7.96; N, 17.92. MS: 234.16 (M + H). IR (KBr, cm^{-1}): 3385.5, 3177, 2937.7, 279.23, 1650.8, 1619.8, 1570, 1457, 1419.5, 1400.7, 1349.7, 1012.9, 852.94, 818.16, 803.3. ^{1}HNMR (DMSO-d_6, 600 MHz) δ 7.89 (s, 1H, $NH_2\alpha$), 7.78 (d, 2H), 7.31 (d, 2H), 7.27 (s, 1H, $NH_2\beta$), 3.45 (s, 2H, CH_2), 2.31 (bs, 8H), 2.11 (s, 3H, CH_3).

*N-(4-Methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)-phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (**1**).* *N*-(5-Bromo-2-methylphenyl)-4-(pyridin-3-yl)-pyrimidin-2-ylamine (**17**) (34.1 g, 0.1 mol), 4-(4-methylpiperazin-1-ylmethyl)benzamide (**18**) (30.3 g, 0.13 mol), cuprous iodide (CuI) (3.81 g, 0.02 mol), potassium carbonate (K_2CO_3) (27.6 g, 0.2 mol), *N*,*N*′-dimethylethylenediamine (DMEDA) (1.32 g, 0.015 mol), sodium *d*-isoascorbate (0.99 g, 0.005 mol), 5 mL of distilled water, and 300 mL of toluene were charged into a reaction flask. The reaction mixture was stirred in air for 24 h, and the temperature was heated to the reflux temperature. The reaction mass was returned to room temperature and

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maintained for 2 h. The solid product was filtered, washed with boiling water (100 mL) and toluene (50 mL), and dried at 60 °C. The crude product was purified by recrystallization from ethylene glycol monomethyl ether to yield *N*-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (**1**) as a light-yellow powder (41.2 g, yield: 83.5%; HPLC purity: 99.9%; genotoxic impurity (**5**) and (**10**): not detected; *o*-toluidine: not detected). Melting point: 206−209 °C. Anal. calcd for $C_{29}H_{31}N_7O$: C, 70.56; H, 6.33; N, 19.86. Found: C, 70.18; H, 6.45; N, 19.32. MS: 494.3 (M + H). IR (KBr, cm^{-1}): 3440.8, 3280.7, 3049.8, 2927.8, 2795.4, 1648, 1577.5, 1534.3, 1451.5, 1418.6, 1372.6, 1351.9, 1289.9, 1261.7, 1204.3, 1163, 1009.7, 923.6, 885.72, 856.53, 808.59, 747.49, 701.43, 646.2. ^{1}H NMR (DMSO-d_6, 600 MHz) δ 10.15 (s, 1H, NH), 9.26 (s, 1H), 8.96 (s, 1H), 8.67 (d, 1H), 8.50 (d, 1H), 8.46 (d, 1H), 8.07 (s, 1H), 7.89 (d, 2H), 7.51−7.41 (m, 5H), 7.19 (d, 1H), 3.51 (s, 2H), 2.37 (bs, 8H), 2.21 (s, 3H), 2.13 (s, 3H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00227.

^{1}H NMR and IR spectra, MS data for each intermediate, and analysis of the content of the standard sample from Sigma-Aldrich and our synthetic imatinib by HPLC and LC-MS (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wangcl@nwu.edu.cn.

ORCID

Cuiling Wang: 0000-0001-7806-1928

Notes

The authors declare no competing financial interest.

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