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A Practical Preparation of Imatinib Base

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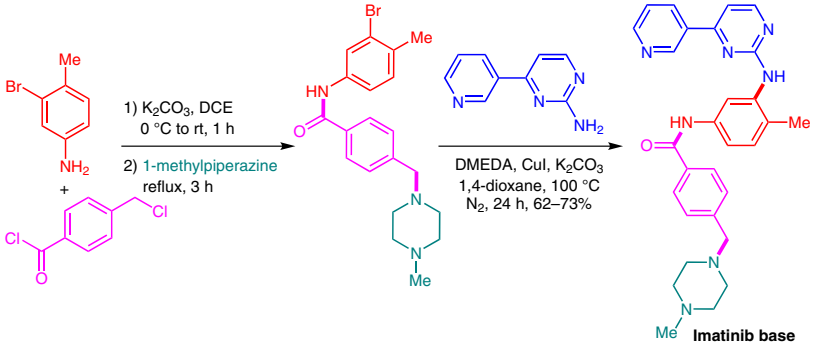

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Abstract A practical preparation of imatinib base was reported in this article. Compared with reported works, the features of this work were the concise procedures, the industrially available starting materials, the avoidance of expensive or highly toxic transition-metal catalysts or reagents, and the genotoxic impurities 6-methyl-*N*[1]-[4-(pyridin-3-yl)pyrimidin-2-yl]benzene-1,3-diamine and 4-(chloromethyl)-*N*-(4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]phenyl)benzamide. The method was scalable to at least 100 mmol, and the products were separated by simple recrystallizations.

Key words practical method, total synthesis, medicinal chemistry, imatinib, copper

Imatinib mesylate (Gleevec, {4-(4-methylpiperazin-1-ylmethyl)-*N*-4-[methyl-3-(4-pyridin-3-yl)pyrimidin-2-yl-amino]phenyl}benzamide methane sulfonate, Figure 1) is an inhibitor of tyrosine kinases that has been approved by the FDA since 7th November, 2001. It is indicated for the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GIST) and attracted much attention in particular due to its positive effects on those patients with CML in recent years.[1]

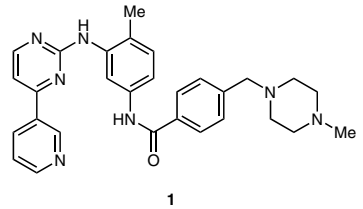

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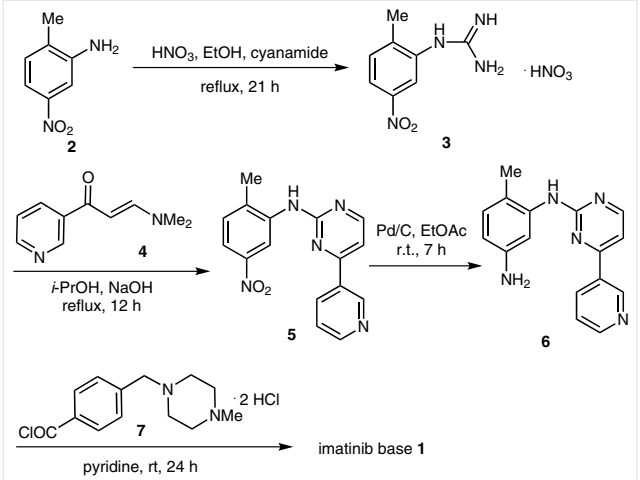
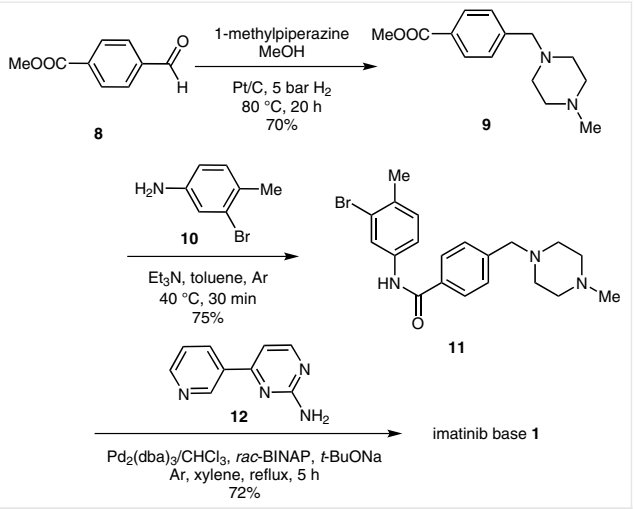
Figure 1 Chemical structure of imatinib base **1**

Generally, there are several typical references on the synthesis of imatinib. The first work was reported by Zimmermann in 1993 (Scheme 1).[2] In their work, 2-methyl-5-nitroaniline (**2**) was chosen as the starting material. Heating **2** with cyanamide in ethanol in the presence of HNO_3 afforded the 1-(2-methyl-5-nitrophenyl) guanidine salt **3**, which led to the intermediate **5** through the reaction with (*E*)-3-(dimethylamino)-1-(pyridin-3-yl)prop-2-en-1-one (**4**). After reduction, **5** was easily transformed to **6**, which afforded the final product **1** through the reaction with **7** (Scheme 1). There are many disadvantages for Zimmermann's synthetic routes and the major defect should be its isolation procedure. Since the processes generated many impurities, flash chromatography was required to isolate the final product from byproducts, limiting the application of this synthetic methodology in large-scale preparation.



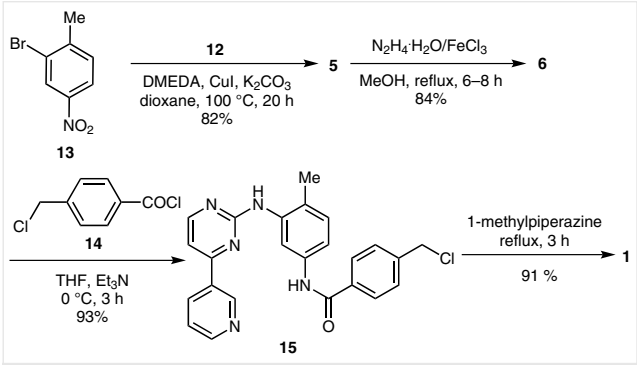
Scheme 1 Zimmermann's routes for the synthesis of imatinib base **1**

Latter, Loiseleur et al. described the second synthetic route for imatinib base **1** by the palladium-catalyzed cross-coupling of 4-(pyridin-3-yl)pyrimidin-2-amine (**12**) with *N*-(3-bromo-4-methylphenyl)-4-[(4-methylpiperazin-1-yl) methyl]benzamide (**11**, Scheme 2).[3] The shortcomings of this synthetic methodology were the special sonication equipment, as well as tedious purification of the product by flash chromatography and separating the desired from the undesired isomers using reverse-phase preparative chromatography. Besides using noble-metal platinum and palladium as catalysts not only enhanced the production cost but also led to the highly toxic metal residual in final product, which should be strictly controlled in the medicine synthesis. Amala et al.,[4] Szakács et al.,[5] Szczepek et al.,[6] and Kompella et al.[7] then improved the above synthetic routes, but there are still shortcomings such as the use of excess moles of tin(II) chloride/Raney nickel and hydrazine hydrate reagents for the reduction of the nitropyrimidine intermediate to prepare the corresponding amino compound **6**. In 2012, Lee et al. tried to improve the last step of Loiseleur's routes using polystyrene-supported CuO as catalyst, but resulted in very low yield of the product imatinib base (15%).[8]



Scheme 2 Loiseleur's routes for the synthesis of imatinib base **1**

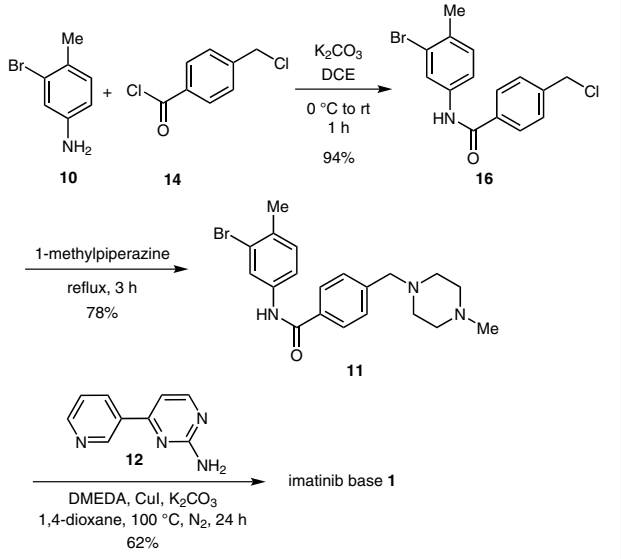
In 2008, Wang et al. reported a new synthetic route to prepare imatinib **1**.[9] As shown in Scheme 3, the method started from 2-bromo-1-methyl-4-nitrobenzene (**13**), an industrially available material. Latter, Lee et al. tried to improve this method using the recyclable polystyrene-supported CuO as catalyst in the coupling of **12** with **13** (Scheme 3).[8] But since copper is not an expensive metal, the easily available inorganic copper salt might be the preferable catalyst from the point of industrial view. The avoidances of noble-metal catalysts made this methodology more practical in large-scale preparation, but the inevitable residual of genotoxic impurities such as the 6-methyl-*N*[1]-[4-(pyridin-3-yl)pyrimidin-2-yl]benzene-1,3-diamine (**6**) and 4-(chloromethyl)-*N*-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)benzamide (**15**) is the major shortcoming of this method.



Scheme 3 Wang's routes for the synthesis of imatinib base **1**

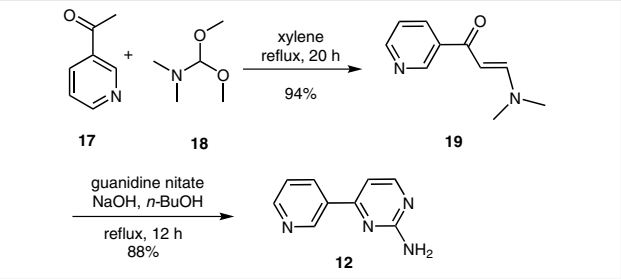
Our group aimed to develop the practical synthetic methodologies with great application potential.[10–11] During our continuous cooperative projects with industrial circles,[11] we recently paid attention to the synthesis of imatinib base because of its huge market prospect in China. Recently, we developed a novel synthetic route for the preparation of imatinib base. Herein, we wish to report our findings.

The major synthetic routes were illustrated in Scheme 4.[12–16] We chose 3-bromo-4-methylaniline (**10**) as the starting material because it was an industrially available chemical with very low price (ca. $16/kg in China). Treating **10** with the cheap reagent 4-(chloromethyl)benzoyl chloride (**14**, ca. $3/kg in China) afforded the intermediate **16** in excellent yield.[13] Compound **16** could be smoothly transformed to the intermediate **11** by refluxing in 1-methylpiperazine.[14] The copper-catalyzed coupling of **11** with **12** led to the final product imatinib base **1** in moderate yield.[15] Compared with Wang's work, this method avoided the generation of the genotoxic intermediates **6** and **15** by adjusting the introduction order of the functional groups. Its last step was very similar to that of Loiseleur's routes (Scheme 2), but considering the fact that copper is less toxic and expensive than palladium,[16] we preferred to choose the copper-catalyzed coupling, although it suffered from the lower product yield. It should be notable that in all of the above procedures, the products could be isolated by recrystallization, which was a very convenient procedure from the point of industrial view. Finally, magnified reactions of **11** with **12** in 100 mmol and 1 mol led to the imatinib base **1** in 73% and 71% yield, respectively, further confirming the practicability of the method.



Scheme 4 Our routes for the synthesis of imatinib base **1**

The price of compound **12** was expensive, but fortunately, it could be synthesized from the industrially available materials through known methodologies:[9] Refluxing 1-(pyridin-3-yl)ethan-1-one (**17**, ca. $72/kg in China) with 1,1-dimethoxy-*N*,*N*-dimethylmethanamine (**18**, ca. $16/kg in China) in xylene led to the intermediate **19** in excellent yield. Further reaction with guanidine nitrate gave 4-(pyridin-3-yl)pyrimidin-2-amine (**12**) in good yield (Scheme 5).[9] Thus, in our procedures, all of the materials were industrially available and their prices were below $100/kg (in China).



Scheme 5 Synthesis of 4-(pyridin-3-yl)pyrimidin-2-amine (**12**)

In order to facilitate the readers to understand the advantages of our routes, we wish to compare them with previously reported works. As shown in Table 1,Zimmermann's routes avoid the genotoxic intermediate **15** generation step, but require noble-metal catalyst and suffer from the genotoxic intermediate **6**. Loiseleur's routes do not undergo the genotoxic intermediates **6** and **15** generation steps, but require both platinum and palladium catalysts, while Lee's improvement using polystyrene-supported CuO catalyst failed and resulted in very low product yield. Free of noble-metal catalyst, Wang's work should be the most practical routes, but unfortunately, it suffers from both of the genotoxic intermediates **6** and **15**. Avoiding noble-metal catalyst and the genotoxic intermediates **6** and **15**, our routes should be more practical and safe.

Table 1 Comparison of the Synthetic Routes for Imatinib Base[a]

Advantages	Noble-metal free	Free of genotoxic **6**	Free of genotoxic **15**
Zimmermann's routes	no	no	yes
Loiseleur's routes	no	yes	yes
Wang's routes	yes	no	no
This work	yes	yes	yes

[a] See Schemes 1–5 for details.

In conclusion, we developed a practical synthetic route for the preparation of imatinib base, which is very practical because of the concise procedures including the practical isolation by recrystallization, the industrially available starting materials and the avoidance of highly toxic transition-metal catalysts or reagents and the genotoxic impurities.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562498.

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(12) **General Methods**
All of the chemicals were industrially pure and directly used without special treatment. Melting points were measured by a WRS-2A digital melting pointing instrument. IR spectra were measured by a Bruker IFS66/S FTIR spectrophotometer. ^{1}H NMR (600 MHz) and ^{13}C NMR NMR (150 MHz) spectra were recorded by using $CDCl_3$ or DMSO-d_6 as the solvent with TMS as the internal standard. Coupling constants (*J*) are given in Hz. Mass spectra were measured on a Thermo Trace DSQ II spectrometer (EI).
(13) **Procedure for the Synthesis of 16**
3-Bromo-4-methylaniline (**10**, 1.86 g, 10 mmol), K_2CO_3 (1.38 g, 10 mmol), and DCE (40 mL) were first added into a 100 mL round-bottom flask and stirred. 4-(Chloromethyl)benzoyl chloride (**14**, 1.89 g, 10 mmol) was then injected. After 1 h, the product **16** precipitated as yellow crystals and could be isolated by filtration and purified by washing with small amount of DCE. About 3.18 g of **16** were obtained (94% yield).
Characterization Data of Compound 16
IR (KBr): 3452, 3284, 2985, 2871, 1641, 1577, 1499, 1441, 1384, 1299, 1137, 1078, 1033, 849, 806, 665 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 7.89 (s, 1 H), 7.85 (d, *J* = 7.8 Hz, 2 H), 7.75 (s, 1 H), 7.51 (d, *J* = 7.8 Hz, 2 H), 7.48 (d, *J* = 7.8 Hz, 1 H), 7.22 (d, *J* = 8.4 Hz, 1 H), 4.63 (s, 2 H), 2.38 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.0, 141.4, 136.6, 134.6, 134.2, 130.9, 129.0, 127.5, 124.9, 123.9, 119.2, 45.3, 22.3 ppm. MS (EI, 70 eV): *m/z* (%) = 339 (10) [M$^+$] (^{37}Cl), 337 (7) [M$^+$] (^{35}Cl), 137 (100). Known compound: CAS Reg. No. 1072105-05-5.[7]
(14) **Procedure for the Synthesis of 11**
To a 100 mL round-bottom flask, **16** (1.7 g, 5 mmol) and 1-methylpiperazine (56 mL) were added. The mixture was refluxed for 3 h and poured to 100 mL of water after cooling to room temperature. The precipitated crystals were filtrated and washed with water to give 1.57 g of **11** as the brown powder (78% yield).
Characterization Data of Compound 11
Mp 140.8–141.3 °C. ^{1}H NMR (600 MHz, DMSO-d_6, TMS): δ = 10.28 (s, 1 H), 8.13 (s, 1 H), 7.90 (d, *J* = 7.8 Hz, 2 H), 7.67 (d, *J* = 8.4 Hz, 1 H), 7.44 (d, *J* = 8.4 Hz, 2 H), 7.32 (s, 1 H), 3.52 (s, 2 H), 2.51–2.35 (br s, 8 H), 2.32 (s, 3 H), 2.15 (s, 3 H) ppm. ^{13}C NMR (150 MHz, DMSO-d_6): δ = 165.4, 142.4, 138.4, 133.2, 132.0, 130.8, 128.6, 127.6, 123.6, 123.2, 119.4, 61.6, 54.7, 52.6, 45.7, 21.7 ppm. Known compound: CAS Reg. No. 581076-59-7.[4]
(15) **Procedure for the Coupling of 11 To Give Imatinib Base 1**
3 mmol Scale Reaction
To a 100 mL round-bottom flask, **12** (0.57 g, 3.3 mmol), **11** (1.2 g, 3 mmol), CuI (0.14 g, 0.75 mmol), and K_2CO_3 (0.83 g, 6 mmol) were added. Under N_2 protection, a solution of DMEDA (66 mg) in 1,4-dioxane (45 mL) was injected. The mixture was stirred at 100 °C for 24 h. After cooling to room temperature, it was poured into a mixture of concentrated NH_3 (12 mL) and sat. NaCl solution (60 mL) and extracted by EtOAc (3 × 50 mL). The combined organic layer was dried by Na_2SO_4 and gave 0.92 g of imatinib base **1** as a white crystal (62% yield) after concentration.
1 mol Scale Reaction
To 20 L autoclave, **12** (189.4 g, 1.1 mol), **11** (402.3 g, 1 mol), CuI (47.8 g, 0.25 mol), and K_2CO_3 (276.4 g, 2 mol) were added. The autoclave was then charged with N_2, and a solution of DMEDA (26.8 mL) in 12 L of 1,4-dioxane was slowly dropped. The mixture was mechanically stirred at 100 °C for 28 h. After cooling to room temperature, it was poured into a mixture of concentrated NH_3 (3.5 L) and cold sat. NaCl solution (15 L, 0–5 °C) and extracted by EtOAc (3 × 14 L). The combined organic layer was dried by Na_2SO_4 and led to white crystal after concentration. The crystal was washed by PE and dried under vacuum overnight to afford 350.5 g of imatinib base **1** in 71% yield.
Characterization Data of Compound 1
Mp 207.4–209.2 °C. IR (KBr): 3410, 3290, 2967, 2964, 2932, 2801, 1628, 1588, 1532, 1507, 1478, 1450, 1416, 1380, 1346, 1007, 829, 761, 700 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6, TMS): δ = 10.22 (s, 1 H), 9.30 (d, *J* = 1.8 Hz, 1 H), 9.02 (s, 1 H), 8.71–8.70 (m, 1 H), 8.54–8.50 (m, 2 H), 8.12 (s, 1 H), 7.93 (d, *J* = 8.4 Hz, 2 H), 7.55–7.44 (m, 5 H), 7.23 (d, *J* = 8.4 Hz, 1 H), 3.53 (s, 2 H), 2.53–2.33 (br s, 8 H), 2.25 (s, 3 H), 2.16 (s, 3 H) ppm. ^{13}C NMR (150 MHz, DMSO-d_6): δ = 165.3, 161.6, 161.2, 159.4, 151.3, 148.1, 142.1, 137.8, 137.2, 134.4, 133.7, 132.2, 130.0, 128.6, 127.5, 123.8, 117.2, 116.8, 107.5, 61.6, 54.7, 52.5, 45.7, 17.6 ppm. Known compound: CAS Reg. No. 152459-95-5.[3]
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