Monatsh Chem (2010) 141:907–911
DOI 10.1007/s00706-010-0334-0

ORIGINAL PAPER

A novel synthesis of imatinib and its intermediates

Haiyan Liu · Wenpin Xia · Yu Luo · Wei Lu

Received: 17 January 2010 / Accepted: 16 May 2010 / Published online: 9 June 2010

Abstract A convenient method has been developed for the synthesis of imatinib and two of its intermediates. *N*-(2-Methyl-5-nitrophenyl)-4-(3-pyridyl)-2-pyrimidinamine, obtained from 2-(methylsulfonyl)-4-(3-pyridyl)pyrimidine via nucleophilic substitution, was reduced by $N_2H_4{\cdot}H_2O$/$FeCl_3{\cdot}6H_2O$/C in 92% yield. The resulting amine was condensed with 4-[(4-methylpiperazin-1-yl)methyl]benzoic acid dihydrochloride, which was prepared from 4-(chloromethyl)benzonitrile via substitution and hydrolysis reactions, to provide the final product imatinib in good yield and high purity.

Keywords Imatinib · 2-(Methylsulfonyl)pyrimidine derivatives · 4-(Chloromethyl)benzonitrile · Substitution

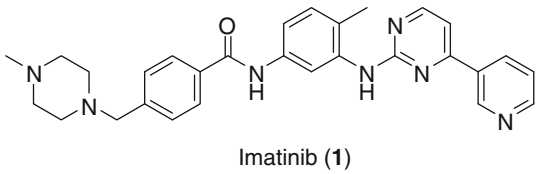
Introduction

Imatinib (formerly called STI-571, 4-[(4-methylpiperazin-1-yl)methyl]-*N*-[4-methyl-3-[4-(pyridin-3-yl)pyrimidin-2-ylamino]phenyl]benzamide, Scheme 1) is a potent and selective inhibitor of BCR-ABL and c-kit tyrosine kinases. It is marketed by Novartis Pharma, and licensed for treatment of chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GISTs), and other types of cancer by the US Food and Drug Administration (FDA) [1–4].

As the first successful targeted drug to treat cancer, imatinib opened the era of molecular targeting therapy and established a model for the development of future drugs. The excellent biological activity and outstanding therapeutic efficacy of imatinib led to enormous interest in its synthesis. In 1993, Zimmermann reported the first synthesis of imatinib [5]. This method used the virulent reagent cyanamide as starting material for the construction of phenylguanidine derivatives; had a low yield; and used a large volume of pyridine that made purification difficult. Loiseleur et al. later developed another synthetic method for imatinib avoiding the use of toxic cyanamide [6], which involved a Buchwald–Hartwig reaction as the key step by employing the expensive catalyst $Pd_2(dba)_3$ and *rac*-BINAP. Subsequently, Liu provided an improved process for the preparation of imatinib [7]. In this protocol, an enaminone reacted with guanidine nitrate to provide pyrimidinylamine, which was then coupled with 2-bromo-1-methyl-4-nitrobenzene in the presence of CuI and *N*,*N*′-dimethylethylenediamine to give key intermediate *N*-(2-methyl-5-nitrophenyl)-4-(3-pyridyl)pyrimidinamine. To date, many other methods for the synthesis of imatinib and its analogs have been reported [8–16]. However, novel synthetic strategies are still needed for two reasons: (1) Many reported synthetic routes have some disadvantages such as lengthy steps, low overall yield, and high production cost; (2) Since many known synthetic routes have been patented, new synthetic methods could circumvent those patented methods. As a part of our ongoing research, we have directed our efforts toward a more practical and novel strategy to synthesize imatinib with simple starting materials and reactions.

Imatinib is a 2-(phenylamino)pyrimidine derivative, and the key step is the construction of *N*-(2-methyl-5-nitrophenyl)-4-(3-pyridyl)-2-pyrimidinamine. In general, 2-aminopyrimidine heterocycles are constructed by condensation reactions of enones with suitable guanidines

H. Liu · W. Xia · Y. Luo · W. Lu (✉)
Department of Chemistry, Institute of Medicinal Chemistry, East China Normal University, Shanghai 200062, People's Republic of China
e-mail: wlu@chem.ecnu.edu.cn



Imatinib (**1**)

Scheme 1

[17–19]. Most of the reported routes have problems of low efficiency, severe pollution, or high cost. It is known that the 2-amino group on the pyrimidine can be conveniently introduced at the C2 position by the displacement of a leaving group with a primary or secondary amine. Many processes used Cl, Br, or sulfone as the leaving group [11, 12], with sulfones proving to be more active than Cl and Br [20–24]. However, 2-sulfonylpyrimidine had never been used as precursor for the generation of *N*-(2-methyl-5-nitrophenyl)-4-(3-pyridyl)-2-pyrimidinamine. Herein we report a novel process for the construction of imatinib and two of its key intermediates (Reagents and conditions: (a) (1) thiourea, Na, ethanol, reflux, 6 h; (2) CH_3I, 1N NaOH, rt, 1 h; (b) $Na_2WO_4{\cdot}H_2O$, 30% H_2O_2, acetone, 40 °C, 10 h; (c) K_2CO_3, DMF, 80 °C, 8–10 h; (d) hydrazine hydrate, $FeCl_3{\cdot}6H_2O$, methanol, reflux, 6 h; (e) K_2CO_3, 1-methylpiperazine, ethanol, reflux, 5 h; (f) conc. HCl, reflux, 8–10 h; (g) 6,CDI, DMF, 70 °C, 10–15 h) (Scheme 2).

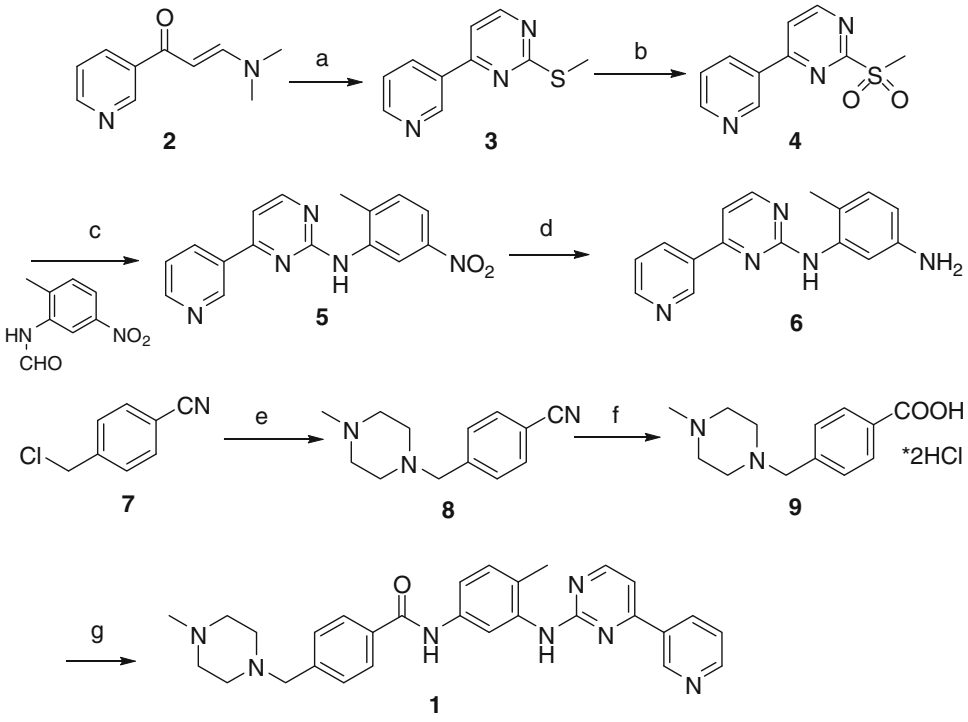
Firstly, the pyrimidine core 2-(methylthio)pyrimidine **3** was generated by reacting enone **2** with thiourea. Secondly, compound **3** was oxidized by H_2O_2 to provide the sulfone **4**, which thus became "activated" and could be displaced with 2-methyl-5-nitroaniline to form the key intermediate *N*-(2-methyl-5-nitrophenyl)-4-(3-pyridyl)-2-pyrimidinamine (**5**). Then compound **5** was reduced to **6** by $N_2H_4{\cdot}H_2O$/$FeCl_3{\cdot}6H_2O$/C. Subsequently, compound **6** was condensed with 4-[(4-methylpiperazin-1-yl)methyl]benzoic acid dihydrochloride, which was prepared efficiently from 4-(chloromethyl)tolunitrile via substitution and hydrolysis reactions, to afford imatinib. This route, which avoids the use of cyanamide and has a good yield, is suitable for the large-scale preparation of imatinib.

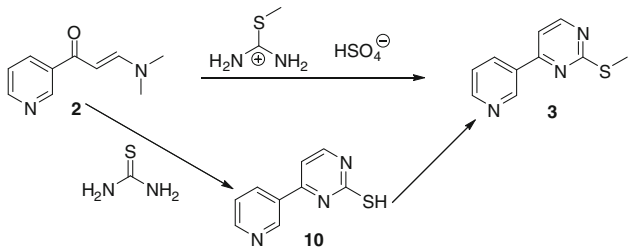
Results and discussion

We initially prepared 2-(methylthio)-4-(3-pyridinyl)pyrimidine (**3**) by a direct cyclization of the enone **2** with *S*-methylisothiourea sulfate but the yield was only 56%. We therefore treated compound **2** with thiourea and Na in ethanol leading to compound **10**, which was S-alkylated with 1.1 equiv. of methyl iodide in dilute aqueous solution of sodium hydroxide at room temperature for 0.5–1 h to provide the desired compound **3** in 87% overall yield (Scheme 3). Obviously, the latter process was more efficient.

Oxidation of sulfide compounds can be achieved by several reagents such as *m*-chloroperbenzoic acid [25–28], acetic acid–H_2O_2 [25, 29], SeO_2–H_2O_2 [30], and oxone [31]. Oxidation of sulfide **3** to sulfone **4** was performed with H_2O_2 and catalytic amounts of sodium tungstate ($Na_2WO_4{\cdot}H_2O$) with high yield of 81%.

Scheme 2





Scheme 3

Initially, compound **5** was synthesized through 2-methyl-5-nitroaniline and 2-(methylsulfonyl)-4-(3-pyridyl)pyrimidine (**4**). However, the yield was unsatisfactory. Compared with the primary amines, N-acylated amines may be more active. Thus, we chose *N*-(2-methyl-5-nitrophenyl)formamide to synthesize compound **5** under the same reaction conditions. As expected, the yield improved from 52 to 88%.

The reduction of nitro compound **5** to the corresponding amine **6** can be achieved [5, 7–9, 15, 32] by employing Fe/HCl, $SnCl_2$/HCl, H_2–Pd/C, or $N_2H_4{\cdot}H_2O$/Pd/C, but the use of Fe/HCl and $SnCl_2$/HCl would cause considerable amounts of waste which would be hard to remove. In our process the nitro compound **5** was reduced by $N_2H_4{\cdot}H_2O$/$FeCl_3{\cdot}6H_2O$ to provide the desired amine **6** in 92% yield. This method gave an excellent yield without unnecessary workup.

As is shown in Scheme 2, 4-(chloromethyl)benzonitrile reacted with 1-methylpiperazine in ethanol in the presence of K_2CO_3 to provide compound **8** in 93% yield, which was then hydrolyzed by 8 M HCl to the target **9** in 96% yield. It should be noted that several previous studies have reported the synthesis of compound **9** by employing 4-(chloromethyl)benzoic acid, methyl 4-(bromomethyl)benzoate, or 4-(bromomethyl)benzonitrile as starting material [32–35], but the overall yields were low (35% [33], 49% in two steps [34], 63% in two steps [35], 58% in three steps [32]). Thus, our two-step procedure with 89% overall yield was much more efficient. Moreover, 4-(chloromethyl)benzonitrile is cheaper by comparison.

Imatinib **1** has generally been constructed via the condensation of *N*-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine (**6**) with 4-[(4-methylpiperazinyl)methyl] benzoyl chloride [5, 36]. However, acid **9** could also be coupled directly with amine **6**. Herein, we report a modified procedure based on a previous method [32], in which the acid **9** reacted with 1,1′-carbonyldiimidazole (CDI), followed by condensation of the acid imidazolide with amine **6** to give imatinib **1** in 91% yield.

Conclusions

In summary, an efficient and promising procedure for the synthesis of imatinib was developed by using two pivotal intermediates: the amine **6**, which could be obtained in four practical steps in 57% overall yield, and the acid **9**, which was prepared from commercially available 4-(chloromethyl)benzonitrile in two steps in 89% overall yield. Furthermore, this approach may offer a practical method for the synthesis of imatinib analogs.

Experimental

^{1}H NMR spectra were recorded on a Bruker DRX-500 (500 MHz). ^{13}C NMR spectra were obtained on a JNM-EX400 (100 MHz). Mass spectra (MS) were determined on a Finnigan MAT-95 mass spectrometer.

2-(Methylthio)-4-(3-pyridyl)pyrimidine (**3**)
Na (4.2 g, 0.18 mol) was dissolved in 200 cm^3 anhydrous ethanol and the solution was stirred for 15 min at room temperature, then 18 g thiourea (0.236 mol) and 42 g 3-(dimethylamino)-1-(3-pyridinyl)-2-propen-1-one (0.218 mol) were added. After being heated for 6 h at 78 °C, the mixture was acidified with acetic acid and heated for 10 min at 78 °C, then cooled to room temperature. A precipitate which formed was collected, washed with water, and dried to give a yellow solid (38.5 g). The product without purification (32 g, 0.169 mol) was dissolved in 200 cm^3 aqueous NaOH (1 M), then 26.4 g methyl iodide (0.186 mol) was added dropwise. The mixture was stirred for 30 min at room temperature; the precipitate formed was filtered and washed with water to give pure **3** as a yellow solid (31.6 g, 86.5% in two steps). M.p.: 105–106 °C (Ref. [37] 94–95 °C).

2-(Methylsulfonyl)-4-(3-pyridyl)pyrimidine
(**4**, $C_{10}H_9N_3O_2S$)
Hydrogen peroxide (30%, 60 cm^3) was added to a solution of 0.6 g sodium tungstate (1.82 mmol) and 30 g compound **3** (0.174 mol) in 200 cm^3 acetone. Then the solution was heated for 10 h at 40 °C, cooled to room temperature, and poured into 80 cm^3 water. After decomposing any remaining hydrogen peroxide by using a saturated aqueous solution of $NaHSO_3$, the solution was extracted with ethyl acetate (3 × 150 cm^3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated to give **4** as a yellow solid (28.2 g, 81%). M.p.: 150–151 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.45$ (s, 3H), 7.54 (m, 1H), 7.99 (d, $J = 5.5$ Hz, 1H), 8.55 (d, $J = 7.5$ Hz, 1H), 8.83 (d, $J = 4.0$ Hz, 1H), 9.01 (d, $J = 5.5$ Hz, 1H), 9.34 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 39.10$, 119.02, 124.06, 130.34, 135.11, 148.61, 153.03, 159.39, 163.80, 166.54 ppm; HRMS (ESI): *m/z* calcd for $C_{10}H_9N_3O_2S$ $[M]^+$ 235.0415, found 258.0308 $[M + Na]^+$.

N-(2-Methyl-5-nitrophenyl)-4-(3-pyridyl)-2-pyrimidinamine (**5**)

To a mixture of 9.34 g *N*-(2-methyl-5-nitrophenyl)formamide (0.052 mol) and 7.88 g K_2CO_3 (0.057 mol) in 30 cm^3 DMF at 80 °C, a solution of 12.2 g compound **4** (0.052 mol) in 10 cm^3 DMF was added and reacted for 8 h at 80 °C. The mixture was cooled to room temperature, poured into an aqueous solution of sodium hydroxide (2 M, 100 cm^3), and stirred for 30 min. The precipitate was filtered and washed with water to give **5** as a yellow solid (14.1 g, 88%). M.p.: 192–193 °C (Ref. [7] 194–195 °C).

N-(5-Amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine (**6**)

To a stirred suspension of 10.0 g compound **5** (32.5 mmol) in 300 cm^3 methanol, 1.3 g iron chloride hexahydrate (4.9 mmol) and 7.7 g hydrazine hydrate (0.13 mol) were added. The reaction mixture was heated for 6 h at 78 °C, then cooled down and charged with 50 mg active carbon. After refluxing for 30 min, the reaction mixture was filtered and washed with hot ethanol. The combined filtrate was then concentrated in vacuo, treated with 200 cm^3 dichloromethane, and the organic layer was washed with 50 cm^3 water and 20 cm^3 brine, dried over anhydrous Na_2SO_4, and evaporated to give **6** as a yellow solid (8.3 g, 92%). M.p.: 137–139 °C (Ref. [9] 134–136 °C).

4-[(4-Methyl-1-piperazinyl)methyl]benzonitrile (**8**)

A solution of 30.0 g 4-(chloromethyl)benzonitrile (0.198 mol) and 12.0 g anhydrous K_2CO_3 (0.087 mol) in 250 cm^3 ethanol was charged with 21.8 g 1-methylpiperazine (0.217 mol). The mixture was heated for 5 h at 78 °C, then cooled to room temperature and filtered. The filtrate was evaporated to give **8** as a white solid (39.0 g, 93%). M.p.: 68–69 °C (Ref. [36] 66–68 °C).

4-[(4-Methylpiperazin-1-yl)methyl]benzoic acid dihydrochloride (**9**)

A solution of 30.0 g compound **8** (0.198 mol) in 50 cm^3 8 M aqueous HCl was heated for 10 h at 100 °C. Then the mixture was cooled to room temperature, and the precipitate was filtered and washed with 200 cm^3 acetone to give **9** as a white solid (37.2 g, 96%). M.p.: 309–311 °C (Ref. [32] 310 °C).

4-[(4-Methylpiperazin-1-yl)methyl]-N-[4-methyl-3-[4-(pyridin-3-yl)pyrimidin-2-ylamino]phenyl]-benzamide (**1**)

To a stirred suspension of 2.0 g compound **9** (6.5 mmol) in 10 cm^3 dry DMF, 1.0 g *N*,*N*′-carbonyldiimdazole (6.2 mmol) was added. The reaction mixture was heated for 2 h at 50 °C. Then 1.3 g amine **6** (4.7 mmol) was added, and the mixture was stirred at 70 °C for another 12 h. After cooling to room temperature, 200 cm^3 water was added to the mixture. The precipitate was filtered, washed with water, dried, and purified with 20 cm^3 ethyl acetate to afford product **1** as an off-white solid (2.1 g, 91%). M.p.: 210–212 °C (Ref. [9] 206–209 °C).

Acknowledgments We gratefully acknowledge the financial support from the Shanghai Science and Technology Mission (10ZR1409600) and the Program for New Century Excellent Talents in University (NCET). We also thank the Laboratory of Organic Functional Molecules, the Sino-French Institute of ECNU for support.

References

1. Druker B, Talpaz M, Resta DJ (2001) N Engl J Med 344:1031
2. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M (2003) N Engl J Med 348:994
3. Druker BJ, Guilhot F, O'Brien SG, Gathmann I, Kantarjian H (2006) N Engl J Med 355:2408
4. Wang SH (2002) J Leukemia Lymphoma 11:29
5. Zimmermann J (1993) EP Patent 0564409
6. Loiseleur D, Kaufmann D, Abel S (2003) WO Patent 2003066613
7. Liu YF, Wang CL, Bai YJ, Han N, Jiao JP, Qi XL (2008) Org Process Res Dev 12:490
8. Kompella A, Bhujanga Rao AKS, Venkaiah Chowdary N (2004) WO Patent 2004108699
9. Szakacs Z, Beni S, Varga Z, Orfi L, Keri G, Noszal B (2005) J Med Chem 48:249
10. Szczepek W, Luniewski W, Kaczmarek L, Zagrodzki B, Samson Lazinska D, Szele Jewski W (2006) WO Patent 2006071130
11. Huang AL, Liu X, Lior Z, Joseph K (2006) US Patent 2006149061
12. Tang CJ, Jia CC (2009) CN Patent 100451015
13. Zimmermann J, Buchdunger E, Mett H (1996) Bioorg Med Chem Lett 6:1221
14. Collins JM, Klecker JRW, Anderson LW (2003) US Patent 20030198594
15. Kankan RN, Rao DR (2004) WO Patent 074502
16. Leonett F, Capaldi C, Carotti A (2007) Tetrahedron Lett 48:3455
17. Breaux EJ, Zwikelmaier KE (1981) J Heterocycl Chem 18:183
18. Schenone P, Sansebastiano L, Mosti L (1990) J Heterocycl Chem 27:295
19. Dorigo P, Fraccarollo D, Santostasi G, Maragno I, Floreani M, Borea PA, Mosti L, Sansebastiano L, Fossa P, Orsini F, Benetollo F, Bombieri G (1996) J Med Chem 39:3671
20. Marchetti F, Sayle KL, Bently J, Clegg W (2007) Org Biomol Chem 5:1577
21. Huang H, Hutta DA, Rinker JM, Hu H (2009) J Med Chem 52:1081
22. Gayo LM, Suto MJ (1997) Tetrahedron Lett 38:211
23. Grant KJ, Jon R, Andrew L, Christophe BB, Richard D, Lambert V (2007) WO Patent 2007085833
24. Zhao LY, Curran PJ, Belanger DB, Hamann B, Reddy PA, Paruch K, Guzi TJ, Dwyer MP, Siddiquim A, Tadikonda PK (2007) WO Patent 2007058942
25. Ruano JLG, Martinez MC, Rodriguez JH, Olefirowicz EM, Eliel EL (1992) J Org Chem 57:4215
26. Spaltenstein A, Carpine PA, Miyake F, Hopkins PB (1987) J Org Chem 52:3759
27. Watanabe M, Koike H, Ishiba T, Okada T, Seo S, Hirai K (1997) Bioorg Med Chem 5:437
28. Fu RZ, Xu XX, Dang Q, Chen F, Bai X (2006) Org Lett 9:571
29. Lotspeich FJ (1965) J Org Chem 30:2068
30. Kim KS, Hwang HJ, Hahn CS (1989) Bull Korean Chem Soc 10:482

31. Webb KS (1994) Tetrahedron Lett 35:3457
32. Ivanov AS, Shishkov SV (2009) Monatsh Chem 140:619
33. Bornmann W, Alauddin M, Gelovani (2008) WO Patent 2008024829
34. Kil KE, Ding YS, Lin KS, Alexoff D, Kim SW, Shea C, Xu YW, Muench L, Fowler JS (2007) Nucl Med Biol 34:153
35. Sairam P, Puranik R, Kelkar AS, Sasikiran S, Veerender M, Parvathi A (2003) Synth Commun 33:3597
36. Zimmermann J, Switzerland W (1996) US Patent 5521184
37. Boully L, Darabantu M, Turck A, Plé N (2005) J Heterocycl Chem 42:1423