An Improved Convergent Approach for Synthesis of Erlotinib, a Tyrosine Kinase Inhibitor, *via* a Ring Closure Reaction of Phenyl Benzamidine Intermediate

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An improved convergent and economical method has been developed for the synthesis of erlotinib, a 4-anilinoquinazoline and an EGFR-tyrosine kinase inhibitor for treatment of non-small-cell lung cancer. The final two steps for the formation of this 4-anilinoquinazoline from suitable 2-aminobenzonitrile intermediate and 3-ethynylaniline were modified and were performed in a simple one-pot reaction. The ring-closing mechanism for the formation of erlotinib from the suitable formamidine intermediate and 3-ethynylaniline was investigated and determined to proceed *via* the formation of phenyl benzamidine intermediate rather than involving Dimroth rearrangement reported earlier. The new benzamidine intermediate was isolated for the first time and characterized.

Introduction

Protein tyrosine kinases are enzymes that play significant roles in signal transduction pathways ranging from stimulation of cell growth and differentiation to arrest of cell proliferation. These enzymes are divided into receptor and non-receptor protein kinases. The receptor tyrosine kinases are themselves distributed among twenty subfamilies.[1] Receptor tyrosine kinases of the epidermal growth factor (EGF) family, which consist of HER-1, HER-2, and HER-3 receptors possess an extracellular binding domain, a trans-membrane domain and an intracellular catalytic (ATP binding) domain.[2] Overexpression and/or inappropriate expression of normal or mutant epidermal growth factor receptor (EGFR) tyrosine kinases have been associated with a number of cancers including non-small-cell lung cancer, breast cancer, colorectal and prostate cancers.[3] As a consequence, small organic molecules or monoclonal antibodies that inhibit EGFR's activity after binding reversibly to intra-cellular catalytic or extracellular binding domains are potential interest as anticancer agents.[4]

4-anilinoquinazoline and its derivatives are a class of potent, selective, reversible and ATP-competitive inhibitors of EGFR tyrosine kinases. Erlotinib 1 (Fig. 1), a 4-anilino-quinazoline, is a potent inhibitor of human EGFR type 1 (HER-1) tyrosine kinase and has been approved by FDA for the second- and third-line treatment of chemo-resistant non-small-cell lung cancer (NSCLS) patients.[5,6] Overexpression of HER-1 tyrosine kinase occurs in 70 to 80% of NSCLS patients and has been linked to increased tumor growth, proliferation, metastasis, angiogenesis, and inhibition of apoptosis.

Erlotinib binds selectively to ATP catalytic domain of HER-1 tyrosine kinase and inhibits EGF-induced phosphorylation thereby restricting the receptor catalytic activity and ultimately preventing cell proliferation.[7] This drug is also in clinical trials for treatment of colorectal cancer,[8] Pancreatic tumor cells,[9] Prostate, Breast and Ovarian cancers.[10-12]

The traditional methods for preparation of 4-anilino-quinazolines such as erlotinib involve the construction of suitable 4-chloroquinazoline intermediate and then reacting of this intermediate with suitable substituted aniline in acidic or basic media.[13,14] The 4-chloro quinazolines are key intermediates and their preparations involve a series of reactions and the use of corrosive and toxic reagents such as phosphorus oxychloride, highly flammable gas such as hydrogen at high pressure, and costly reagents such platinum oxide.[15]

Recently Reddy *et al.* reported a novel convergent approach for synthesis of erlotinib and gefitinib which involves the construction of suitable formamidine intermediates.[16] The formamidine intermediates, which were prepared *via* a series of reactions, then reacted with suitable substituted
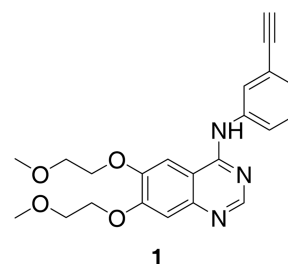

Figure 1. Structure of erlotinib **1**.

anilines in acetic acid at 130 °C to form erlotinib and gifitinib in moderate yields. Although the novel convergent method avoids the use of 4-chloroquinazolines, the method suffered from lower yields in final key steps of preparation of 4-anilinoquinazoline products. The lower yields of the final steps were due to decomposition of both valuable formamidine intermediates and costly substituted anilines at high temperature as well as the tedious purification process of 4-anilinoquinazoline products. Therefore, we believe there is a need for improved convergent process to prepare these potent and selective 4-anilinoquinazoline molecules. The new convergent method should significantly improve the yield of final products, improve the work up and purification processes of the final steps, and should reduce the number of steps if possible.

Herein, we report an improved convergent process for synthesis of erlotinib hydrochloride starting with 3,4-dihydroxy benzoic acid in eight steps with overall yield of 60%. The method in general uses inexpensive starting materials, and in some cases reaction conditions has been modified to reduce the number of synthetic steps and obtain high yields. The two key steps for the formation of the 4-anilinoquinazoline **1** from suitable 2-aminobenzonitrile intermediate **7** and 3-ethynylaniline were modified and these steps were performed in a simple one-pot reaction. The yield of the final ring closure step, the most crucial step, was improved significantly. The formation of erlotinib **1** from formamidine intermediate **8** and 3-ethynylaniline was investigated and determined by NMR and IR to proceed through formation of another phenyl benzamidine intermediate **9** rather than involving Dimroth rearrangement proposed by Reddy *et al.*[16] The phenyl benzamidine intermediate **9** was isolated for the first time and characterized by NMR and IR. Moreover, the conversion of 3,4-bis(2-methoxyethoxy)-benzoic acid to 3,4-bis(2-methoxyethoxy)-benzonitrile was achieved for the first time in a simple one-pot reaction using urea and phosphorus pentoxide, thereby avoiding the use of expensive, highly toxic, and unstable reagents such as Deoxo-fluor,[17] PCl$_5$,[17] and diphosphorus tetraiodide[18] for this transformation.

Experimental

General. Melting points were uncorrected and obtained on an Electrothermal 9100 apparatus. Infrared spectra were recorded using a shimadzu (8400) FT-IR spectrometer. Column chromatography was performed using silica gel 60 (230-400 mesh) as stationary phase and eluting with distilled hexane and ethyl acetate. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMRs were recorded on a Bruker Avance (AC 80) instrument. CDCl$_3$ and DMSO-d_6 were used as NMR solvents. Chemical shifts were reported in parts per million (ppm) downfield from internal tetramethylsilane (TMS). All reactions were monitored by thin layer chromatography (TLC, R_f values) using silica gel 60 coated plates F$_{254}$ (Merck, aluminum sheets). Visualization was performed by ultraviolet light at 254 and 354 nm. HPLC was performed at room temperature using a waters 2489 instrument, hichrom

C18 columns, acetonitrile/water: 70/30 (0.01% TFA) as a mobile phase. Mass spectra were obtained by using a waters LC/MS ZQ 2000 instrument. Solvents and reagents were either used as supplied.

3,4-Bis(2-methoxyethoxy)-benzoic acid (4). A suspension of 3,4-dihydroxy benzoic acid (20.0 g, 0.13 mol), potassium carbonate (71.8 g, 0.52 mol) and tetrabutylammonium iodide (4.8 g, 0.013 mol) in DMF (240 mL) was stirred for 1 h at 100 °C. The reaction mixture was cooled to 50 °C, and then 1-chloro-2-methoxyethane (47.2 mL, 0.52 mol) was added and the reaction mixture was heated to 85 °C and stirred for 20 h at this temperature. The reaction mixture was cooled to room temperature, and the solid material was filtered and washed with ethyl acetate (300 mL). The combined filterates were evaporated under reduced pressure to afford a yellow residue (ester product). Without any further isolation and purification, the ester residue was dissolved in a solution of methanol (210 mL), water (70 mL) and potassium hydroxide (21.85 g, 0.39 mol) and stirred for 4 h at room temperature. Methanol was removed under reduced pressure, and the pH of the solution was adjusted to ~3 by adding a solution HCl (2 N) at 0 °C. A solid was precipitated which was filtered, washed with cold water, and dried (Na$_2$SO$_4$) to afford carboxylic acid **4** (34.4 g, 98%) as a white solid; R_f (20% *n*-hexane/ethyl acetate) 0.25; mp 108-110 °C. FT-IR ν$_{max}$ (KBr) 2981, 2933, 2921, 1666 (C=O), 1596, 1442, 1278, 1234, 871, 763 cm^{-1}; ^{1}H NMR (CDCl$_3$) 7.62-7.57 (dd, 1H, *J* = 8.4 Hz, *J* = 1.9 Hz, H-Ar), 7.53-7.51 (d, 1H, *J* = 1.9 Hz, H-Ar), 6.86-6.82 (d, 1H, *J* = 8.4 Hz, H-Ar), 4.15-4.11 (m, 4H, 2 CH$_2$O), 3.74-3.69 (m, 4H, 2 CH$_2$O), 3.38 (s, 6H, 2 OCH$_3$); ^{13}C NMR (CDCl$_3$) 165.13, 152.55, 139.12, 124.35, 121.83, 116.27, 111.54, 73.89, 70.76, 61.62; *m/z* (ES$^+$) 271.26.

3,4-Bis(2-methoxyethoxy)-benzonitrile (5). A mixture of 3,4-bis(2-methoxyethoxy)-benzoic acid (30.0 g, 0.11 mol) and urea (60.1 g, 1.0 mol) were heated to 220 °C and stirred for 30 min at this temperature. A small aliquot of reaction mixture was taken, added water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na$_2$SO$_4$, evaporated in vacuum to afford a white solid residue. The residue was evaluated by FT-IR and mass spectroscopy and determined to be 3,4-bis(2-methoxyethoxy)-benzamide intermediate. R_f (5% methanol/ethyl acetate) 0.48; mp 115-118 °C FT-IR ν$_{max}$ (KBr) 3550 (N-H), 3466 (N-H), 2990, 1750 (C=O), 1453, 1376, 795, 690 cm^{-1}; *m/z* (ES$^+$) 270.31.

The remainder of reaction in the same pot was then suspended in xylene (250 mL), added phosphorus pentoxide (46.9 g, 0.33 mol) and the mixture was heated to reflux for 18 h. The reaction mixture was cooled to 80 °C and filtered. The solid material was washed with hot ethyl acetate (200 mL), and combined filterates were washed with saturated solution of sodium bicarbonate (3 × 50 mL), dried over Na$_2$SO$_4$ and concentrated in vacuum to obtain benzonitrile **5** (25.2 g, 90%) as a yellow oil; R_f (5% methanol/ethyl acetate) 0.85; FT-IR ν$_{max}$ (solution in CH$_2$Cl$_2$) 2927, 2883, 2223 (CN), 1514, 1421, 1271, 1248, 864, 780 cm^{-1}; ^{1}H NMR

An Improved Convergent Approach for Synthesis of Erlotinib

Bull. Korean Chem. Soc. **2011**, Vol. 32, No. 3   911

(CDCl$_3$) 7.50-7.46 (dd, 1H, J = 8.0 Hz, J = 1.9 Hz, H-Ar), 7.40-7.36 (d, 1H, J = 1.9 Hz, H-Ar), 6.92-6.86 (d, 1H, J = 8.0 Hz, H-Ar), 4.17-4.13 (m, 4H, 2 CH$_2$O), 3.74-3.69 (m, 4H, 2 CH$_2$O), 3.33 (s, 6H, 2 OCH$_3$); ^{13}C NMR (CDCl$_3$) 152.45, 139.20, 123.85, 121.87, 118.50, 116.07, 112.41, 73.89, 70.72, 61.68; *m/z* (ES$^+$) 252.29.

4,5-Bis(2-methoxyethoxy)-2-nitrobenzonitrile (6). A solution of 3,4-bis(2-methoxyethoxy)-benzonitrile (30.0 g, 0.12 mol) in glacial acetic acid (25 mL) was added drop wise to a solution of nitric acid 65% (85 mL) at 0 °C in 4 h. Temperature was raised to 50 °C and stirred for 4 h. The reaction mixture was cooled to 25 °C and poured on ice-water (300 mL). The precipitate was formed which was filtered, washed with cold water, *n*-hexane (325 mL) and dried on air to afford benzonitrile **6** [20] (32.0 g, 90%) as a yellow solid; R_f (ethyl acetate) 0.6; mp 135-136 °C; FT-IR ν_{max} (KBr) 2930, 2888, 2223 (CN), 1512, 1533, 1384, 1262, 1241, 879, 670 cm^{-1}; ^{1}H NMR (CDCl$_3$) 7.87 (s, 1H, H-Ar), 7.10 (s, 1H, H-Ar), 4.20-4.02 (m, 4H, 2 CH$_2$O), 3.77-3.68 (m, 4H, 2 CH$_2$O), 3.31 (s, 6H, 2 OCH$_3$); ^{13}C NMR (CDCl$_3$) 152.41,151.56, 144.41, 123.91, 121.87, 118.42, 100.12, 73.81, 70.72, 61.68; *m/z* (ES$^+$) 297.27.

2-Amino-4,5-bis(2-methoxyethoxy)-benzonitrile (7). To suspension of 4,5-bis(2-methoxyethoxy)-2-nitrobenzonitrile (30.0 g, 0.10 mol) in water (350 mL) was added sodium dithionite (70.3 g, 0.40 mol) and the reaction mixture was heated to 50 °C and stirred at this temperature for 3 h. Then, the temperature was raised to 65 °C and concentrated HCl (130 mL) was added drop wise in 30 min. The reaction mixture was cooled to 20 °C and the pH was adjusted to ~10 using 50% aqueous sodium hydroxide solution. The product was extracted with ethyl acetate (350 mL) and combined organic phases were washed with brine and dried over Na$_2$SO$_4$. Evaporation of the solvent under high vacuum afforded of 2-amino-4,5-bis(2-methoxyethoxy)-benzonitrile [16] (24.6 g, 90%) as a brown solid; R_f (ethyl acetate) 0.45; mp 72-73 °C; FT-IR ν_{max} (KBr) 3454 (N-H), 3361 (N-H), 2929, 2889, 2220 (CN), 1521, 1436, 1269, 1234, 1128, 867 cm^{-1}; ^{1}H NMR (CDCl$_3$) 6.91 (s, 1H, H-Ar), 6.26 (s, 1H, H-Ar), 4.20-4.04 (m, 4H, 2 CH$_2$O), 3.79-3.70 (m, 4H, 2 CH$_2$O), 3.44 (s, 6H, 2 OCH$_3$); ^{13}C NMR (CDCl$_3$) 152.27, 150.95, 141.35, 124.03, 121.93, 115.22, 90.52, 73.87, 70.79, 61.73; *m/z* (ES$^+$) 267.30.

6,7-Bis(2-methoxyethoxy)-*N*-(3-ethynylphenyl)-quinazolin-4-amine (1). To a reaction flask equipped with a condenser and a Dean-Stark apparatus were added 2-amino-4,5-bis(2-methoxyethoxy)-benzonitrile (35.0 g, 0.13 mol), toluene (350 mL), acetic acid (0.5 mL), and DMF-DMA (34.8 mL, 0.26 mol). The reaction mixture was heated to 105 °C and stirred for 4 h. A small aliquot of the reaction mixture was taken, and toluene and volatile compounds were completely stripped off under reduced pressure to obtain *N'*-[2-cyano-4,5-{bis(2-methoxyethoxy)phenyl}]-*N,N*-dimethyl formamidine (8) as a brown oil[16]; R_f (ethyl acetate) 0.42; FT-IR ν_{max} (solution in CH$_2$Cl$_2$) 2935, 2813, 2220 (CN), 1634, 1600, 1565, 1455, 1269, 1234, 1128, 866 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.53 (s, 1H, H-formamidine), 7.00 (s, 1H,

H-Ar), 6.46 (s, 1H, H-Ar), 4.19-4.07 (m, 4H, 2 CH$_2$O), 3.80-3.71 (m, 4H, 2 CH$_2$O), 3.42 (s, 6H, 2 OCH$_3$), 3.04 (s, 6H, 2 NCH$_3$); ^{13}C NMR (CDCl$_3$) δ 152.71, 152.66, 150.51, 143.03, 117.98, 117.26, 104.91, 95.85, 69.94, 69.65, 68.53, 67.33, 58.22, 58.12, 39.23, 33.49; *m/z* (ES$^+$) 322.37.

The remainder of the reaction in the same pot was subjected to vacuum distillation and excess DMF-DMA and small volume of toluene (~50 mL) were removed from the reaction mixture. Then, the reaction mixture was cooled to room temperature and added 3-ethynylaniline (15.2 g, 0.13 mol) and acetic acid (14.9 mL, 0.26 mol). The reaction mixture was stirred at 60 °C for 5 h. Then, the temperature was raised to reflux and the reaction was stirred for 5 h. The reaction mixture was cooled to room temperature, quenched in crushed ice/water (500 mL) and adjusted pH ~7 with ammonia solution. The light brown precipitate was formed, isolated, and washed with cold water (200 mL) and *n*-hexane (200 mL). The brown residue was dissolved in hot ethyl acetate and decolorized (charcoal). Evaporation of the solvent under reduced pressure afforded yellow solid residue. The residue was then recrystallized from methanol to give erlotinib **1** (47.0 g, 90%); R_f (5% methanol/ethyl acetate) 0.55; mp 152-153 °C; FT-IR ν_{max} (KBr) 3251, 3069, 2929, 2893, 1502, 1463, 1429, 1332, 1255, 1217, 1130, 851cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.67 (s, 1H, H-Ar), 7.88 (s, 1H, H-Ar), 7.79 (s, 1H, H-Ar), 7.66 (d, J = 8.0 Hz, 1H, H-Ar), 7.19-7.40 (m, 3H, H-Ar), 4.23 (m, 4H, 2 CH$_2$O), 3.81 (m, 4H, 2 CH$_2$O), 3.45 (s, 6H, 2 OCH$_3$), 3.12 (s, 1H, ethynyl); ^{13}C NMR (CDCl$_3$) 168.11, 158.48, 154.17, 151.23, 146.44, 142.32, 129.19, 123.27, 122.09, 121.13, 116.46, 112.73, 108.22, 99.37, 82.4, 79.76, 72.18, 69.72, 52.33; m/z (ES$^+$) 394.47.

6,7-Bis(2-methoxyethoxy)-*N*-(3-ethynylphenyl)-quinazolin-4-amine hydrochloride (2). Erlotinib **1** (40.0 g, 0.10 mol) was dissolved in hot methanol (500 mL). The solution was cooled to 15-20 °C and was passed through dry hydrochloric acid gas for 3 min keeping the temperature of the reaction mixture at 15-20 °C. The solid precipitate was formed, filtered and dried at 50 °C to afford erlotinib hydrochloride **2** [16] (41.0 g, 94%) as a yellow solid; R_f (20% methanol/ethyl acetate) 0.22; mp 228-229 °C; FT-IR ν_{max} (KBr) 3276, 3056, 3020, 2921, 2896, 2819, 2746, 2711, 1667, 1564, 1512, 1446, 1284, 1122, 892 cm^{-1}; ^{1}H NMR (DMSO-d_6) 11.45 (s, 1H, NH), 8.81 (s, 1H, H-Ar), 8.30 (s, 1H, H-Ar), 7.90-7.72 (m, 2H, H-Ar), 7.53-7.33 (m, 3H, H-Ar), 4.45-4.25 (m, 4H, 2 CH$_2$O), 3.79-3.70 (m, 4H, 2 CH$_2$O), 3.40 (s, 1H, ethynyl), 3.25 (s, 6H, 2 OCH$_3$); ^{13}C NMR (DMSO-d_6) 170.22, 159.11, 155.07, 151.20, 147.28, 142.31, 130.89, 125.76, 124.35, 122.34, 117.65, 114.15, 108.83, 100.97, 86.76, 80.63, 75.78, 73.52, 51.25.

4,5-Bis(2-methoxyethoxy)-*N*-(3-ethynylphenyl)-2-((*E*)-formamido) benzamidine (9). 3-ethynylaniline (0.18 g, 1.5 mmol) was added to a solution of formamidine 8 (0.5 g, 1.5 mmol), and acetic acid (0.09 mL, 1.5 mmol) in toluene (5 mL). The resulting solution was stirred at 60 °C for 5 h. The reaction mixture was cooled to room temperature and poured onto the pad of silica gel and eluted with ethyl acetate/n-hexane (9:1) to obtain phenyl benzamidine **9** as a

yellow solid; R_f (ethyl acetate) 0.35; FT-IR ν_{max} (KBr) 3487-3056 (broad), 2935, 2820, 2113 (ethynyl), 1630, 1600, 1568, 1455, 1269, 1234, 1128, 866 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.72 (s, 1H, H-formamidine), 7.71 (s, 1H, H$_6$-Ar), 7.66 (d, 1H, $J_{4,5}$ = 8.0 Hz, H$_4$-Ar), 7.63 (s, 1H, H$_2$-Ar), 7.56 (t, 1H, $J_{5,6}$ = 8.0 Hz, $J_{5,4}$ = 8.0 Hz, H$_5$-Ar), 7.44 (d, 1H, $J_{6,5}$ = 8.0 Hz, H$_6$-Ar), 7.02 (s, 1H, H$_3$-Ar), 5.64 (brs, 2H, NH), 4.27-4.23 (m, 4H, 2 CH$_2$O), 3.83-3.78 (m, 4H, 2 CH$_2$O), 3.41 (s, 6H, 2 OCH$_3$), 3.22 (s, 1H, ethynyl), 3.02 (s, 6H, 2 NCH$_3$); ^{13}C NMR (CDCl$_3$) δ 174.30 (C-benzamidine), 152.99 (C-formamidine), 152.84 (C-Ar), 148.06 (C-Ar), 142.65 (C-Ar), 139.71 (C-Ar), 136.07 (C-Ar), 132.66 (C-Ar), 130.69 (C-Ar), 129.54 (C-Ar), 127.43 (C-Ar), 123.90 (C-Ar), 108.59 (C-Ar), 106.36 (C-Ar), 80.63 (C-ethynyl), 78.75 (C-ethynyl), 69.69 (C-O), 69.50 (C-O), 67.76 (C-O), 67.48(C-O), 58.17 (C-O), 58.10 (C-O), 39.71 (C-NCH$_3$), 36.07 (C-NCH$_3$); m/z (ES$^+$) 439.52.

Results and Discussion

The synthesis of erlotinib **1** (Scheme 1) was started from 3,4-dihydroxy benzoic acid. *O*-alkylation of 3,4-dihydroxy benzoic acid with 4.0 equivalent of 1-chloro-2-methoxy-ethane in hot DMF afforded intermediate methoxyethoxy-3,4-bis(2-methoxyethoxy)-benzoate in quantitative yield.

DMF was then removed and basic hydrolysis of the ester was performed in the same batch to afford the 3,4-bis(2-methoxyethoxy)-benzoic acid in 98% overall yield. No further purification was performed in this step. The conversion of carboxylic acid **4** to corresponding nitrile **5**, one of the key intermediates, was carried out in a simple one-pot reaction of carboxylic acid **4**, urea and phosphorus pentoxide as a dehydrating agent. In this step, first carboxylic acid **4** reacted with urea at 220 °C for 30 min to produce 3,4-bis(2-methoxyethoxy)-benzamide. The dehydration of amide compound was carried out in the same pot using P$_2$O$_5$ as dehydrating agent in refluxing xylene to afford nitrile **5** with no further purification in 90% yield. The nitration of 3,4-bis(2-methoxyethoxy)-benzonitrile in nitric acid and glacial acetic acid at 0 °C afforded the single nitro product **6** in 90% yield. No purification was performed in this step. The reduction of the nitro group of **6** using sodium dithionite in acidic solution gave 2-amino-4,5-bis(2-methoxyethoxy)-benzonitrile in 90% yield. No purification was necessary in this step.
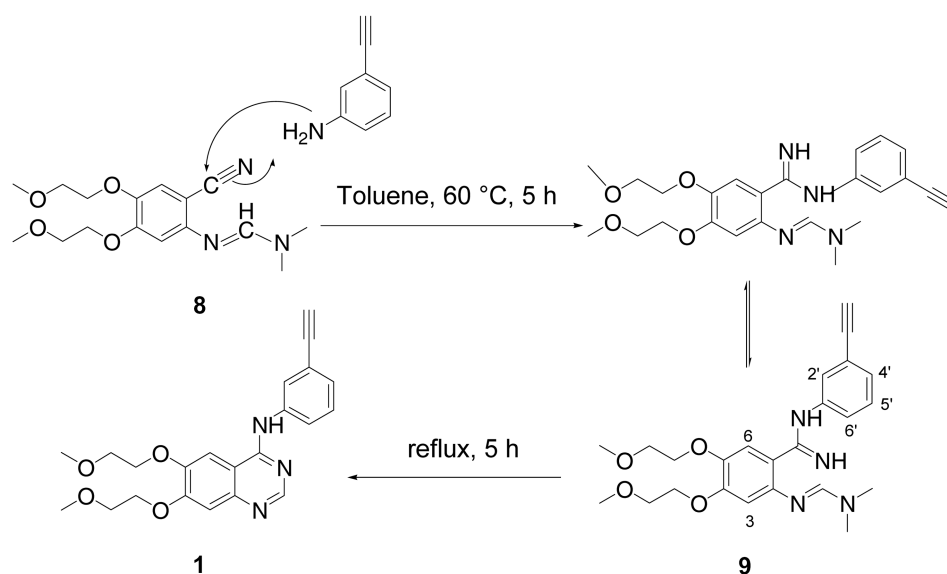
The mechanism of the formation of 4-anilinoquinazoline from suitable formamidine intermediates and substituted anilines has been reported earlier by Reddy *et al.* to proceed through Dimroth rearrangement (Scheme 2).[16,19] For example, the formation of erlotinib has been proposed to
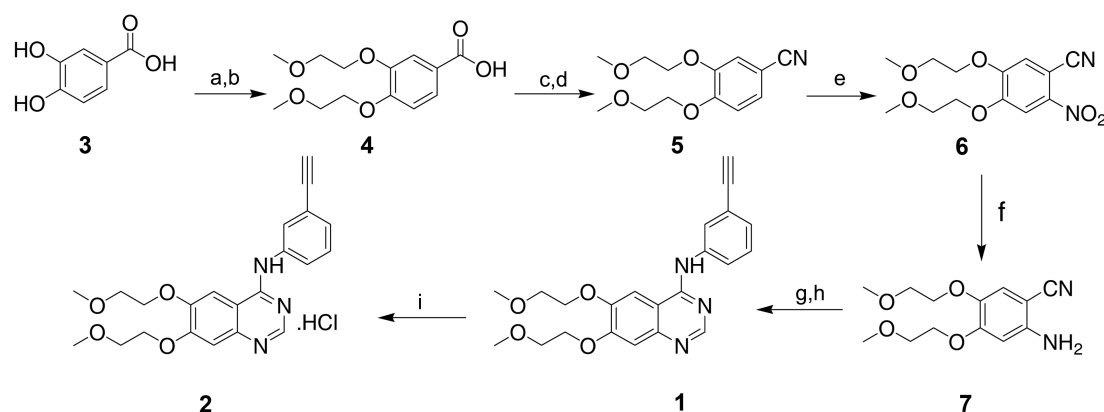
Scheme 1. (a) K$_2$CO$_3$, ClCH$_2$CH$_2$OCH$_3$, TBAI, DMF, 85 °C, 20 h. (b) KOH, CH$_3$OH, H$_2$O, 4 h, 98%. (c) Urea, 30 min, 210-220 °C. (d) P$_2$O$_5$, xylene, reflux, 18 h, 90%. (e) HNO$_3$, glacial acetic acid, 0 °C, 4 h, 90%. (f) Na$_2$S$_2$O$_4$, H$_2$O, HCl (aq), 3 h, 90%. (g) DMF-DMA, acetic acid, toluene, 105 °C, 4 h. (h) 3-ethynylaniline, acetic acid, toluene, 60 °C, 5 h, then reflux, 5 h, 90%. (i) HCl gas, CH3OH, 15-20 °C, 94%.
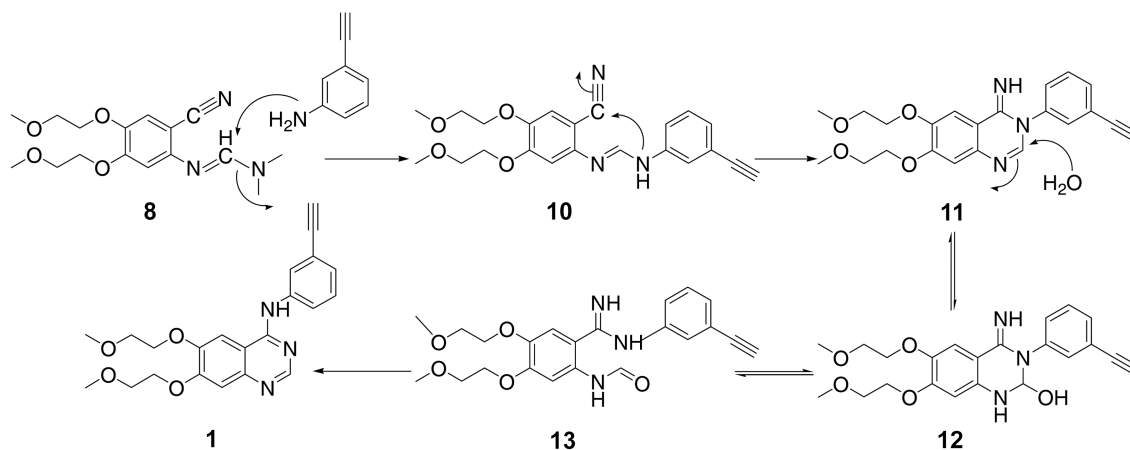
Scheme 2. Proposed ring closure mechanism of formamidine intermediates and substituted anilines by Reddy *et al.*[16,19]

Scheme 3. Ring closure mechanism of formamidine intermediate **8** and 3-ethynylanilines.

proceed through the formation of intermediate **10**, cyclization of intermediate **10** to form imine **11** followed by the hydrolysis of pyrimidine ring at C-N$_3$ bond to form intermediate **13,** and finally the ring closure reaction.[16]

However, by monitoring the reaction mixture of formamidine intermediate **8** and 3-ethynylaniline first at room temperature and then at 125 °C by TLC and LC/MS, novel phenyl benzamidine intermediate **9** was the only intermediate which was identified and isolated (Scheme 3). The phenyl benzamidine intermediate **9** is not reported in literature, and it is the first time we report the isolation and characterization of the important intermediate **9** by NMR, IR and LC/MS. None of the proposed intermediate **10** or **13** was observed by LC/MS during the reaction. Heating the intermediate **9** in acetic acid or in the mixture of toluene and acetic acid afforded erlotinib **1**. The ring closing mechanism of formamidine intermediate **8** and 3-ethynylanilines was determined to proceed *via* intermediate **9** rather than Dimroth rearrangement.

By determining the ring closure mechanism of formamidine intermediate **8** and 3-ethynylaniline, we were able to modify the reaction conditions and significantly improve yield of formation of erlotinib. First, the final two steps of this process were performed in a simple one-pot reaction. In this manner, 2-amino benzonitrile **7** was treated with DMF-DMA in toluene and acetic acid to produce formamidine intermediate **8**. Excess DMF-DMA was then removed by vacuum distillation and 3-ethynylaniline and acetic acid were added to the same pot containing the formamidine intermediate **8**. The reaction mixture was heated to 60 °C for 5 h to produce phenyl benzamidine intermediate **9**.

Finally, heating the phenyl benzamidine intermediate **9** in refluxing toluene and acetic acid produced the 4-anilinoquinazoline in high yield. It should be noted that it is necessary to run the reaction first at 60 °C to allow the complete formation of phenyl benzamidine intermediate and

then to raise the temperature to 125 °C for ring closure and obtain product **1**. Heating the formamidine intermediate **8** and 3-ethynylaniline directly at 125-130 °C in toluene and acetic acid also produced the erlotinib **1** in 66% yield as reported earlier.[16] However, the remainder of reaction (~25-35%) was neither the valuable formamidine intermediate nor the costly 3-ethynylaniline. A few other side products (not isolated) that we believe they are due to decomposition of both the formamidine intermediate and 3-ethynyl aniline at high temperature (125-130 °C) were observed by TLC. Moreover, the presence of theses side products complicated the isolation and recrystallization techniques and reduced the final yield. On contrary, the phenyl benzamidine intermediate **9** formed by the foramidine **8** and 3-ethynyl aniline at 60 °C is much more stable and once formed, it was converted to 4-anilinoquinazoline in significantly higher yield at refluxing toluene. Finally, the erlotinib free base treated with HCl gas to obtained erlotinib hydrochloride.

Conclusion

An improved convergent, efficient and economical method has been described for the synthesis of erlotinib hydrochloride. The final step involving the ring closing mechanism of formamidine intermediate **8** and 3-ethynylanilines was investigated and determined to proceed *via* a novel phenyl benzamidine intermediate **9** rather than Dimroth rearrangement proposed earlier by Reddy *et al*. The intermediate **9** was characterized by NMR, IR and LC/MS. Finally, the key two steps of the formation the erlotinib were modified and were run in a simple one-pot procedure and the yield was significantly improved.

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